Universidade de Aveiro Escola Superior de Saúde
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Efeitos da reabilitação respiratória em doentes hospitalizados por exacerbação aguda da DPOC

Effects of hospital-based pulmonary rehabilitation in acute exacerbations of COPD

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Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Fisioterapia, realizada sob a orientação científica da Doutora Alda Marques, Professora Adjunta da Escola Superior de Saúde da Universidade de Aveiro, e co-orientação da Mestre Ana Oliveira, Professora Assistente Convidada da Escola Superior de Saúde da Universidade de Aveiro.

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O júri

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palavras-chave Exacerbações, reabilitação respiratória, hospital.

resumo

Enquadramento: A reabilitação respiratória (RR) apresenta grau A de recomendação para doentes com doença pulmonar obstrutiva crónica (DPOC) estável. No entanto, em doentes hospitalizados com exacerbação aguda da DPOC (EADPOC) o seu efeito é ainda controverso.

Objetivos: Contribuir para o estabelecimento dos efeitos da RR em doentes hospitalizados com EADPOC.

Métodos: Foi realizado um estudo piloto de intervenção pré-pós no Centro Hospitalar de Leiria. Os doentes foram avaliados 24 a 48 horas após estabilização clínica (*baseline*) e na alta hospitalar, tendo-se recolhido a seguinte informação: frequência respiratória por observação, frequência cardíaca e saturação periférica de oxigénio com um oxímetro, pressão arterial (PA) com um esfigmomanómetro, dispneia com a escala modificada Medical Research Council (mMRC), dispneia e fadiga em repouso com a escala de Borg modificada (mBorg), impacto da doença com o questionário *COPD Assessement Test* (CAT), força de preensão e do quadricípite com dinamómetros, força dos músculos respiratórios com um medidor de pressões respiratórias, funcionalidade com o Short Physical Performance Battery (SPPB) e tolerância ao exercício com o teste de levantar-e-sentar em 1 minuto (1'STST). Um programa de RR composto por controlo respiratório e higiene brônquica, exercício e apoio psicoeducacional (entrega de panfletos com alguns temas importantes: controlo respiratório e posições de alívio da dispneia, higiene brônquica, infecções do tracto respiratório inferior e exercício) foi aplicado, 5 dias por semana, durante o tempo de hospitalização. Três meses após a alta, rehospitalizações e visitas ao serviço de urgência foram anotadas. Comparações entre a *baseline* e a alta hospitalar foram realizadas com os testes de Wilcoxon, os tamanhos de efeito (ES) foram calculados e, sempre que possível, o número e a percentagem de doentes que melhoraram acima da mínima diferença clinicamente importante (MDCI) foram determinados.

Resultados: Quinze doentes hospitalizados com diagnóstico de EADPOC (14 homens; 71,2±7,2 anos; 46,1± 20,6% do prevista do Volume Expiratório Máximo no primeiro segundo) foram incluídos. Os doentes estiveram hospitalizados 13±4,3 dias e realizaram 4,7±2 sessões de RR. Após a alta, melhorias significativas foram encontradas na dispneia em repouso (ES=-0,976, p=0,008), PA (PA sistólica, ES=-1,584, p=0,016; PA diastólica, ES=-1,231, p=0,008) e na CAT (ES=-0,925, p=0,01). Nenhuma diferença significativa foi encontrada nas restantes medidas. A maioria das medidas apresentou uma melhoria em pelo menos 50% dos doentes. Melhorias acima do MDCI foram observadas em 8 (80%) doentes na dispneia em repouso avaliada com a mBorg, 7 (70%) na CAT, 6 (60%) na mMRC, 6 (60%) no 1'STST e 5 (50%) na pontuação total do SPPB. Nenhum evento adverso foi relatado. Três meses após a alta, seis doentes visitaram o serviço de urgência e desses seis, quatro foram novamente hospitalizados devido a EADPOC.

Conclusão: Um programa de RR em doentes hospitalizados por EADPOC parece ser seguro e eficaz. Mas uma vez que aproximadamente 40% dos doentes voltou a ter de usar os serviços de saúde até aos 3 meses de *follow-up*, alerta-se para a necessidade de continuar a apoiar estes doentes na comunidade para minimizar a necessidade de recorrer aos hospitais. Este estudo demonstrou melhorias similares aos benefícios já reconhecidos da RR em doentes estáveis com DPOC mas estudos seguindo metodologias mais robustas são necessários para confirmar estes resultados.

keywords Exacerbations, pulmonary rehabilitation, inpatients.

abstract

Background: Pulmonary rehabilitation (PR) has grade A of recommendation for patients with stable chronic obstructive pulmonary disease (COPD). However, the effect of PR in hospitalised patients with acute exacerbation of COPD (AECOPD) is still controversial.

Aim: To contribute for determining the effects of PR in hospitalised patients with AECOPD.

Methods: A pre-post intervention pilot study was conducted in the *Centro Hospitalar de Leiria*. Patients were evaluated 24-48 hours after clinical stabilisation (baseline) and at discharge. The following information was collected: respiratory rate by observation, heart rate and oxygen saturation with an oximeter, blood pressure (BP) with a sphygmomanometer, dyspnoea with the modified Medical Research Council dyspnoea questionnaire (mMRC), dyspnoea and fatigue at rest with modified Borg scale (mBorg), the impact of the disease with the COPD Assessment test (CAT), handgrip and quadriceps muscle strength with dynamometers, respiratory muscle strength with respiratory pressure meter, functionality with Short Physical Performance Battery (SPPB) and exercise tolerance with 1-minute sit-to-stand test (1'STST). A PR programme composed of breathing retraining and airway clearance techniques, exercise training and psychoeducational support (delivery of flyers with important information: breathing control and positions for dyspnoea relief, airway clearance techniques, lower respiratory tract infections and exercise), was implemented 5 days per week during hospitalisation. Three months after discharge, rehospitalisations and visits to the emergency service were noted. Comparisons between baseline and discharge were performed with the Wilcoxon signed-rank tests, effect sizes (ES) were calculated and whenever possible, the number and percentage of patients that improved above the minimal clinically important difference (MCID) was determined.

Results: Fifteen inpatients diagnosed with AECOPD [14 male; 71.2±7.2y; 46.1±20.6% of predicted of forced expiratory volume in one second (FEV_1)] were enrolled. Patients were hospitalised 13±4.3 days and concluded 4,7±2 sessions of PR. After discharge, significant improvements were found in dyspnoea at rest (ES=-0.976, p=0.008), BP (systolic BP, ES=-1.584, p=0.016; diastolic BP, ES=-1.231, p=0.008) and CAT (ES=-0.925, p=0.01). No significant differences were found in the remaining outcome measures. Most of the outcome measures improved in at least 50% of the patients. Improvements above the MCID were observed in 8 (80%) patients on dyspnoea at rest assessed with the mBorg, 7 (70%) on the CAT, 6 (60%) on the mMRC, 6 (60%) on the 1'STST and 5 (50%) on SPPB total score. No adverse events were reported. Three months after discharge, 6 patients visited the emergency service and of these 6, 4 were hospitalised due to a re-exacerbation of the COPD.

Conclusions: Hospital-based PR seems to be a safe and effective intervention in patients with an AECOPD. Nonetheless, since approximately 40% of the patients required health services within 3 months of follow-up, it becomes clear that support of these patients needs to be continued in the community to minimise the necessity to resort to hospitals. This study provided similar improvements to the already recognised benefits of PR in stable patients with COPD, nevertheless studies with more robust methodologies are needed to confirm these results.

Abbreviations and/or acronyms

1'STST - 1-minute sit-to-stand test
6MWT – 6-minute walk test
AECOPD – acute exacerbation of chronic obstructive pulmonary disease
ATS – American Thoracic Society
BMI – body mass index
BP – blood pressure
CAT – COPD Assessment test
CCI – Charlson Comorbidity Index
COPD – chronic obstructive pulmonary disease
ERS – European Respiratory Society
ES – effect sizes
FEV_1 – forced expiratory volume in one second
FVC – forced vital capacity
GOLD – Global Initiative for Chronic Obstructive Lung Disease
HHD – hand-held dynamometry
HR – heart rate
mBorg – modified Borg scale
MCID – minimal clinically important difference
MEP – maximal expiratory pressure
MIP – maximal inspiratory pressure
mMRC – modified Medical Research Council dyspnoea questionnaire
PA – physical activity
PR – pulmonary rehabilitation
QMS – quadriceps muscle strength
RR – respiratory rate
SGRQ – St. George Respiratory Questionnaire
SpO2 – peripheral oxygen saturation
SPPB – Short Physical Performance Battery

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1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is “a common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases” (The Global Initiative for Chronic Obstructive Lung Disease, 2018; Vogelmeier et al., 2017). Currently, COPD is the 3rd leading cause of morbidity and mortality worldwide, resulting in a significant and increasing health, economic and social burden (Vestbo et al., 2013; World Health Organization, 2018). Although still an underdiagnosed disease (Gibson, Loddenkemper, Sibille, & Lundbäck, 2013; World Health Organization, 2017), COPD affects approximately 384 million people worldwide (The Global Initiative for Chronic Obstructive Lung Disease, 2018) and 800.000 in Portugal (Observatório Nacional das Doenças Respiratórias, 2015).

Patients with COPD suffer about 2-3 acute exacerbations of COPD (AECOPD) per year (G C Donaldson, Seemungal, Bhowmik, & Wedzicha, 2002; Hurst et al., 2010; Seemungal, Donaldson, Bhowmik, Jeffries, & Wedzicha, 2000; Spencer, Calverley, Burge, & Jones, 2004), and in Portugal these events are responsible for 1/3 of all hospitalisations due to respiratory disease (Observatório Nacional das Doenças Respiratórias, 2017). Acute exacerbations of COPD are defined as an acute worsening of respiratory symptoms that result in additional therapy and can be classified as: mild (treated with short acting bronchodilators only, SABDs); moderate (treated with SABDs plus antibiotics and/or oral corticosteroids); or severe (patients require hospitalisation or visits to the emergency room) (The Global Initiative for Chronic Obstructive Lung Disease, 2018).

Few studies have demonstrated that frequent exacerbators (i.e., patients who have two or more exacerbations per year) have more severe airway obstruction (Gupta, Govidagoudar, Yadav, & Agarwal, 2018; Kim et al., 2016; S. J. Lee et al., 2012), higher scores in the modified Medical Research Council dyspnoea questionnaire (mMRC) (Gupta et al., 2018; S. J. Lee et al., 2012) and in the COPD Assessment Test (CAT) (Kim et al., 2016), demonstrating a reduction on health status, which contributes to the worsening of symptoms and increase susceptibility to new exacerbations (G C Donaldson et al., 2002; Gupta et al., 2018; Hurst et al., 2010; Seemungal et al., 2000; Spencer et al., 2004). Additionally, previous history of exacerbations (Kim et al., 2016), presence of specific comorbidities and a high number of comorbidities have been found

to be risk factors for new AECOPD and hospitalisations (Putcha, Drummond, Wise, & Hansel, 2015; Smith & Wrobel, 2014; Soler-Cataluna et al., 2005; The Global Initiative for Chronic Obstructive Lung Disease, 2018). Severe exacerbations lead to significant declines on exercise capacity and muscle strength (Pitta et al., 2006), which are good and reliable predictors of re-hospitalisations (Emtner, Arnardottir, Hallin, Lindberg, & Janson, 2007) and lower survival in patients with COPD (Garcia-Aymerich, Lange, Benet, Schnohr, & Antó, 2006), resulting in a significant burden of patients' health status (O'Reilly, Williams, & Rice, 2007) and increased health expenditures (Hoogendoorn, 2011; O'Reilly et al., 2007).

It has been shown that strategies for preventing and early treating AECOPD may reduce the health burden, morbidity and mortality associated with complications from AECOPD (G C Donaldson et al., 2002; Seemungal et al., 1998). In exacerbations requiring hospitalisation some therapeutic strategies can modify the disease progression (Spencer et al., 2004; J. A. Wedzicha, Singh, & Mackay, 2014), and by reducing the duration of the exacerbation symptoms, the risk of new exacerbations is also reduced, increasing the interval between them (G. C. Donaldson et al., 2015), and consequently reducing the economic burden of COPD (Hoogendoorn, 2011). Thus, AECOPD prevention and treatment is currently one of the main focus of attention for national and international health policies makers and researchers (Centers for Disease Control and Prevention, 2011; Programa Nacional para as Doenças Respiratórias, 2017; M. A. Puhan, Gimeno-Santos, Cates, & Troosters, 2016; Reid et al., 2012; Jadwiga A. Wedzicha, Calverley, et al., 2017).

One of the non-pharmacologic treatments of AECOPD currently being studied is pulmonary rehabilitation (PR) (Ali, Talwar, & Jain, 2014; Carr, Hill, Brooks, & Goldstein, 2009; Clini et al., 2009; Deepak, Mohapatra, Janmeja, Sood, & Gupta, 2014; He, Yu, Wang, Lv, & Qiu, 2015; Ko et al., 2011; Liao, Chen, Chung, & Chien, 2015; Man, Polkey, Donaldson, Gray, & Moxham, 2004; Murphy, Bell, & Costello, 2005; M. A. Puhan et al., 2016; M. A. Puhan et al., 2012; Seymour et al., 2010; Tang, Blackstock, Clarence, & Taylor, 2012). PR is defined by the American Thoracic Society [ATS] and European Respiratory Society (ERS) as "a comprehensive intervention based on a thorough patient assessment followed by patient tailored therapies that include, but are not limited to, exercise training, education, and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours" (Spruit, Singh, et al., 2013). PR has a grade A of recommendation for patients with COPD in a stable phase (Bolton

et al., 2013), and has demonstrated to improve patients' symptoms, exercise capacity, quality of life (American Thoracic Society, 1999; Lacasse, Goldstein, Lasserson, & Martin, 2006; McCarthy et al., 2015; Nici et al., 2006; Spruit, Singh, et al., 2013), and physical and emotional participation in everyday activities (American Thoracic Society, 1999; McCarthy et al., 2015; The Global Initiative for Chronic Obstructive Lung Disease, 2018). However, the effect of PR during a hospitalisation due to an AECOPD is still unclear (M. A. Puhan et al., 2016; Spruit et al., 2018; Jadwiga A. Wedzicha, Miravitlles, et al., 2017).

Studies in patients hospitalised with AECOPD reported that an early PR may be feasible and safe to implement (Clini et al., 2009; He et al., 2015), and appears to reduce symptoms (Clini et al., 2009; Liao et al., 2015; Martin-Salvador et al., 2016), improve exercise capacity (Ali et al., 2014; Clini et al., 2009; Liao et al., 2015), quality of life (Ali et al., 2014), and produce improvements in the musculoskeletal system, contradicting the deterioration caused by immobilisation during hospitalisation (Martin-Salvador et al., 2016). However, studies on PR in this population are still performed with poorly robust methodologies (M. A. Puhan et al., 2016; Jadwiga A. Wedzicha, Miravitlles, et al., 2017). Some studies have only investigated the effects of exercise training (Reid et al., 2012; Tang et al., 2012) in hospitalised patients, others studied the effects of community-based PR after hospital discharge (Deepak et al., 2014; Man et al., 2004) and others included two settings (inpatients and outpatients) in the same group that was being studied (Carr et al., 2009; Eaton et al., 2009), making conclusions about the effects of PR during AECOPD difficult to establish.

Therefore, the effects of PR during hospitalisation due to AECOPD are still uncertain, namely on some important measures, such as functionality, a vital outcome for patients' daily life, which is severely impaired during AECOPD (Chin, 2017; Haughney et al., 2005) and one of the main concerns of patients (Haughney et al., 2005). This uncertainty, limits optimisation of results and may be hindering the quality of the health care that can be delivered to patients with AECOPD and their families. It is believed that establishing the effects of PR in hospitalised patients with AECOPD will contribute to a better management of these patients.

Thus, this study aimed to implement a PR programme in hospitalised patients with AECOPD and determine its effects in vital signs, peripheral oxygen saturation (SpO_2), dyspnoea, impact of the disease, peripheral and respiratory muscle strength,

functionality, exercise capacity and hospitalisations and visits to the emergency service after 3 months of hospital discharge.

2. METHODS

This study is part of a larger study entitled “GENIAL – Genetic and clinical markers in COPD trajectory”, funded by *Programa Internacional de Competitividade e Internacionalização* – POCI, through *Fundo Europeu de Desenvolvimento Regional* – FEDER (POCI-01-0145-FEDER-007628), *Fundação para a Ciência e Tecnologia* (PTDC/DTP-PIC/2284/2014) and under the project UID/BIM/04501/2013.

2.1. STUDY DESIGN

A pre-post intervention pilot study was conducted in the *Centro Hospitalar de Leiria, Leiria, Portugal,* in hospitalised patients diagnosed with AECOPD.

2.2. ETHICAL CONSIDERATIONS

Ethical approval was previously obtained from the Ethics Committee and the Administrative Board of the *Centro Hospitalar de Leiria* (acta nº 01 of 2018.01.09 – Annex I). Prior to any data collection, written and verbal information (Appendix A) about the study was provided and written informed consent (Appendix B) was collected from every patient.

2.3. PATIENTS’ RECRUITMENT

One hospital centre was contacted. Meetings were arranged with the directors of the four services of the hospital centre that could be involved in the study (Physical and Rehabilitation Medicine, Pneumology, Internal Medicine 1 and 2), to explain its purposes and clarify any doubts. After the meetings, written permissions to conduct the study in the four services were obtained and the documentation was sent to the ethical commission and the administration board of the *Centro Hospitalar de Leiria*. Recruitment started when formal approval was obtained from the ethics committee.

Patients with AECOPD were recruited while hospitalised in the *Centro Hospitalar de Leiria*. Patients were eligible if they were: i) hospitalised with an AECOPD, diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (The Global Initiative for Chronic Obstructive Lung Disease, 2018); ii) clinically stable,

according to the medical team and iii) capable of giving written informed consent. Exclusion criteria included: i) the presence of significant cardiac, musculoskeletal and/or neuromuscular disease that could prevent collaborating in evaluations and/or treatments; ii) the presence of haemoptysis, pneumothorax, pulmonary oedema, or other respiratory complications not exclusively due to the AECOPD; iii) need for invasive or non-invasive mechanical ventilation 24 hours a day; iv) signs of cognitive impairment and v) history of neoplasia or immune disease.

According to the recommendations for adequate sample sizes to conduct pilot studies, 12 patients would be required to conduct this study (Julious, 2005). However, as it is known that dropout rates in respiratory interventions are around 30-35% (Garrod, Marshall, Barley, & Jones, 2006), 16 patients were aimed to be recruited.

2.4. Data Collection

Data collection occurred between January and August 2018, in the ward where each patient was hospitalised.

Eligible patients were contacted by the researcher 24 to 48 hours after clinical stabilisation, according to the medical team. Patients who agreed to participate were assessed at baseline (24-48h after clinical stabilisation) and at discharge.

The strict confidentiality and anonymity of all data collected were ensured. Data collected were protected with a code, and only researchers had access to the database and patient's data.

2.4.1. Measures and Procedures

Sociodemographic, anthropometric, general clinical data, and cardiorespiratory parameters were collected in the presented order with a structured questionnaire, to characterise the sample and complement the respiratory assessment. These data were collected by the researcher using information from the electronic clinical process when possible, and through individually assessment in order to capture a holistic perspective of each patient.

Sociodemographic data included age, gender, years of education, marital status and occupation. Anthropometric data involved weight and height measurements to calculate the body mass index (BMI). General clinical data included smoking habits, comorbidities,

medication used, oxygen therapy, non-invasive ventilation, hospitalisations and visits to the emergency service in the past year, respiratory crisis, dyspnoea, self-reported physical activity and the impact of the COPD in the well-being and everyday life of the patient.

Height (in metres - m) and weight (in kilograms - kg) were measured to calculate the BMI. Patients were encouraged to perform the measurements without shoes and wearing as fewer clothes as possible. Height and weight were measured in a JOFRE® mechanical weight and height scale to the nearest 0.1 kg and 0.5 cm. The BMI was calculated by dividing the weight in kilograms by the square of the height in metres (kg/m^2) (American College of Sports Medicine, 2014; Cervi, Franceschini, & Priore, 2005; World Health Organization). Values between 18.5-24.9 kg/m^2 are considered normal; values below 18.5 kg/m^2 represent underweight, values between 25-29.9 kg/m^2 represent pre-obesity and values over 30 kg/m^2 are classified as obesity (World Health Organization). The BMI is a good nutritional status indicator for adults (World Health Organization) and older people (Cervi et al., 2005). Respiratory function can be compromised by both obesity and severe malnourishment. Malnourished patients have weaker respiratory muscles which are more likely to fatigue (Main & Denehy, 2016). Overweight and obese patients with mild to moderate COPD have shown a higher prevalence of the most dominant comorbid disorders, i.e., hypertension, osteoarthritis, diabetes and heart failure (OR: 1.4–1.7; OR: 2.4–3.8 and OR: 2.3 respectively) (Verberne et al., 2017).

Comorbidities were analysed using the Charlson Comorbidity Index (CCI) (Charlson, Pompei, Ales, & MacKenzie, 1987). The CCI is a simple, valid and reliable method to classify the severity of comorbidities considering both the number and the seriousness of comorbidities, weighting which comorbidity according to its potential to influence on mortality (Austin, Wong, Uzzo, Beck, & Egleston, 2015; Charlson et al., 1987; de Groot, Beckerman, Lankhorst, & Bouter, 2003; Huang et al., 2014; Quan et al., 2011). It was calculated according to the scoring system established by Charlson et al. (1987), and patients were divided into three groups: mild, with CCI scores of 1–2; moderate, with CCI scores of 3–4; and severe, with CCI scores ≥5 (Huang et al., 2014). This index is a useful measure as it condenses comorbidity information into easy to use metrics (Austin et al., 2015; Quan et al., 2011), and for prognostic stratification purposes, it is better than merely counting the number of comorbidities (Charlson et al., 1987). The CCI presented good-to-excellent discrimination in predicting in-hospital mortality (Quan et al., 2011), correlation coefficients exceeding 0.40 (de Groot et al., 2003), and good test-retest

reliability and moderate to good interrater reliability (de Groot et al., 2003). This is the most extensively studied comorbidity index (Austin et al., 2015; Charlson et al., 1987; de Groot et al., 2003; Huang et al., 2014; Quan et al., 2011), and has been used to predict the risk of mortality in various disease subgroups, such as COPD (Karoli & Rebrov, 2012), type 2 diabetic nephropathy (Huang et al., 2014), renal disease (Hemmelgarn, Manns, Quan, & Ghali, 2003), stroke (Hemmelgarn et al., 2003), intensive care (Poses, McClish, Smith, Bekes, & Scott, 1996; Quach et al., 2009), liver disease (Myers, Quan, Hubbard, Shaheen, & Kaplan, 2009) and heart failure (D. S. Lee et al., 2005).

Dyspnoea is the perception of an unpleasant and/or uncomfortable sensation of breathing that can only be described by the subject (Parshall et al., 2012). During daily activities, dyspnoea was measured with the mMRC scale (Bestall et al., 1999; Crisafulli & Clini, 2010; Direcção Geral de Saúde, 2013; Spruit, Singh, et al., 2013; The Global Initiative for Chronic Obstructive Lung Disease, 2018). The mMRC is a simple, valid and widely used method in PR to discriminate and characterise populations or stratify patients with different lung function impairment (Bestall et al., 1999; Crisafulli & Clini, 2010) based on their sensation of breathing difficulty during daily life activities (Bestall et al., 1999; Crisafulli & Clini, 2010). A Portuguese version of mMRC scale is available at the *Direção-Geral de Saúde* (Direcção Geral de Saúde, 2013) website and it contains five grades in a scale from 0 to 4, with grade 4 representing the greatest dyspnoea impairment (Crisafulli & Clini, 2010; Direcção Geral de Saúde, 2013; The Global Initiative for Chronic Obstructive Lung Disease, 2018). According to the GOLD (2018), patients with a mMRC grade superior or equal to 2 are labelled as “more breathlessness” and those with scores inferior to 2 as “less breathlessness” (The Global Initiative for Chronic Obstructive Lung Disease, 2018). The minimal clinically important difference (MCID) has been established as a variation of 1 grade for stable patients with COPD after PR (Crisafulli & Clini, 2010; de Torres et al., 2002) and as a variation of 0.5 for patients with AECOPD after pharmacological treatment (A. Oliveira, Machado, & Marques, 2018).

Dyspnoea and fatigue were also measured at rest with the modified Borg scale (mBorg) (G. Borg, 1998; G. A. Borg, 1982; Kendrick, Baxi, & Smith, 2000; Spruit, Singh, et al., 2013; Wilson & Jones, 1989). The mBorg is a quick, easy to use, valid, reliable and responsive assessment tool to obtain a patient’s subjective state of dyspnoea (Kendrick et al., 2000; Spruit, Singh, et al., 2013). In patients with COPD, it is most commonly used in clinical practice for assessing symptoms of dyspnoea and fatigue (Bausewein, Farquhar, Booth, Gysels, & Higginson, 2007). The mBorg is a vertical scale from 0 to 10, where 0 means no perception of symptom at all and 10 a maximal perception of difficulty

in either breathing or fatigue, with a total of 12 points, 10 of which are anchored by simple and understandable verbal expressions of progressively increasing intensity (G. Borg, 1998; G. A. Borg, 1982; Kendrick et al., 2000; Wilson & Jones, 1989). Patients were asked to rate their perceived dyspnoea and fatigue by selecting the number with the corresponding words that most appropriately described their symptoms (Kendrick et al., 2000), while sitting and resting for at least 10 minutes. The MCID for dyspnoea symptoms in the mBorg has been stablished as a variation of 2 points for stable patients with COPD after PR (Crisafulli & Clini, 2010; Ries, 2005) and a variation of 1 point for patients with AECOPD after pharmacological treatment (A. Oliveira et al., 2018).

Level of physical activity (PA) was measured with the brief physical activity (Brief-PA) tool (Marshall, Smith, Bauman, & Kaur, 2005). The Brief-PA tool assesses the frequency and duration of moderate and vigorous PA undertaken in an "usual" week through 2 questions (Marshall et al., 2005). Each question is scored from 0 to 4 and the total score consists of summing up the result of the two questions, ranging from 0 to 8 (Marshall et al., 2005). Patients with scores of 0-3 are classified as "insufficiently active", and patients with scores higher or equal to 4 as "sufficiently active" (Marshall et al., 2005). The Brief-PA is a quick, valid (k=0.40, 95% confidence interval [CI]: 0.12-0.69) and reliable (k=0.53, 95% CI: 0.33-0.72) (Marshall et al., 2005) tool with good percentage agreement (71%) to measure PA of patients with COPD and identifying insufficiently active patients who may need PA advice (Cruz, Jácome, & Marques, 2017; Marshall et al., 2005). The total score was demonstrated to be significantly correlated with the international PA questionnaire ($r=0.523$, $p<0.001$), accelerometer ($r=0.529$, $p<0.001$) and daily steps ($r=0.565$, $p<0.001$) (Cruz et al., 2017).

The impacts of COPD on patients' life was assessed with the CAT (Direcção Geral de Saúde, 2013; The Global Initiative for Chronic Obstructive Lung Disease, 2018). A Portuguese version of the CAT is available at the *Direção-Geral de Saúde* (Direcção Geral de Saúde, 2013) website. The CAT has 8 items, scored from 0 to 5, and the total score is calculated by summing up the scores in each item (Direcção Geral de Saúde, 2013; P. W. Jones et al., 2009; Silva, Morano, Viana, Magalhaes, & Pereira, 2013; The Global Initiative for Chronic Obstructive Lung Disease, 2018). A total score below 10 is classified as "reduced impact", scores between 10-20 as "medium impact", 21-30 "high impact" and scores above 30 were classified as "very high impact" (Direcção Geral de Saúde, 2013). This is a short, simple, sensitive to changes in health status and a commonly used worldwide questionnaire in patients with COPD (Direcção Geral de Saúde, 2013; P. W. Jones et al., 2009; Silva et al., 2013; The Global Initiative for Chronic

Obstructive Lung Disease, 2018). It has been demonstrated to be a valid, reliable and standardised measure of COPD health status with worldwide relevance (P. W. Jones et al., 2009), excellent intra-rater and inter-rater reliability (intraclass correlation coefficient [ICC] = 0.96; 95% CI: 0.93-0.97; p<0.001; and ICC=0.98; 95% CI: 0.96-0.98; p<0.001, respectively) and good test-retest reliability according to Bland & Altman plots (Silva et al., 2013). The total score of the CAT was demonstrated to have a significant correlation with forced expiratory volume in one second (FEV_1) (r=-0.38; p=0.006) and forced vital capacity (FVC) (r=-0.39; p=0.005) in litres, 6-minute walk test (6MWT) distance (r=-0.37, p=0.008), St. George Respiratory Questionnaire (SGRQ) scores (r=0.51-0.54; p<0.001), mMRC (r=0.48; p<0.001), and with the depression scores of the hospital anxiety and depression scale (r=0.39; p=0.001) (Silva et al., 2013). The MCID has been established as a variation of 2 points for patients with AECOPD receiving pharmacological treatment (Kon et al., 2014).

A detailed cardiorespiratory assessment was performed to collect objective data on vital signs [respiratory and heart rates (RR and HR, respectively) and blood pressure (BP)], SpO_2, lung function (FEV_1, FVC, and FEV_1/FVC ratio), peripheral and respiratory muscular strength (knee extensors, handgrip, and respiratory pressures), lower extremity function and exercise capacity.

Before the performance of the cardiorespiratory assessment tests, vital signs and SpO_2 were assessed while patients were sitting and resting for at least 10 minutes. Respiratory rate is the most useful sign that a patient's breathing is compromised, and it was assessed as the number of respiratory cycles in a minute with the patient resting comfortably and being unaware of the measurement (Main & Denehy, 2016). The normal adult RR is approximately 12–16 breaths/minute (Main & Denehy, 2016). Heart rate, SpO_2 and BP were collected with a patient monitor (Qube®, Spacelabs Healthcare, Snoqualmie, Washington, United States). Normal values of HR in adults are between 60-100 beats/minute (Main & Denehy, 2016). In patients with AECOPD, SpO_2 has been shown to have high sensitivity and specificity to detect both hypoxemia (sensitivity=83.9%, specificity=88.9%) and hypercapnia (sensitivity=71.3%, specificity=76%), with a strong positive correlation with partial pressure of oxygen (PaO_2) (r=0.80; p<0.001) and a strong negative correlation with partial pressure of carbon dioxide ($PaCO_2$) (r=-0.74; p<0.001) (Guryay et al., 2007). Blood pressure was measured by placing a sphygmomanometer cuff around the right upper arm, except when patients had catheters in the right arm. Normal adult systolic BP ranges between 90-140 mmHg and the diastolic BP between 60-95 mmHg (Main & Denehy, 2016).

Lung function was assessed through spirometry (The Global Initiative for Chronic Obstructive Lung Disease, 2018), a non-invasive, reproducible and objective measure of airflow limitation (The Global Initiative for Chronic Obstructive Lung Disease, 2018). It was performed using a portable spirometer (Micro I v1.00, CareFusion, UK) according to the international ATS/ERS guidelines (Miller et al., 2005) and the values of FVC, FEV_1 and FEV_1/FVC ratio were obtained. The patient performed the manoeuvre in the sitting position, with a nose clip, and was encouraged to perform a maximal inspiration, followed by a blast of exhalation, maintaining the exhalation until completely breathing out (Miller et al., 2005). The manoeuvre was first demonstrated to the patient. Three measurements were performed and the best was considered for analysis (Miller et al., 2005).

All patients were classified accordingly to the GOLD grades and stages (The Global Initiative for Chronic Obstructive Lung Disease, 2018). The GOLD stages were determined with the ABCD assessment tool based on the number of exacerbations in the previous year and mMRC collected at the baseline assessment (The Global Initiative for Chronic Obstructive Lung Disease, 2018), as it better discriminates the PA of daily living, including the sedentary behaviour (Munari et al., 2017).

Muscular strength of the knee extensors, ahead designated as quadriceps muscle strength (QMS), was assessed with a hand-held dynamometry (HHD - Hoggan MicroFET2, Hoggan Scientific, U.S.A.) (Bohannon, 1997) in kilogram of force (kgf). The HHD allows the assessment of muscle strength in a simple, easy and portable way, providing quantification of strength (O'Shea, Taylor, & Paratz, 2007; Stark, Walker, Phillips, Fejer, & Beck, 2011). Patients were asked to sit on the table, with the knee and hip at 90 degrees, and with her/his hands on the table. The HHD was placed on the anterior side of the tibia with its lower edge at the level of the malleoli and resistance was applied in the direction of flexion, matching the patient force. Patients were asked to extend their leg and gradually increase the force applied to a maximum over 3–5 seconds (Bohannon, 1997; Eisner, Iribarren, et al., 2008). Three measurements were performed on the dominant side and the best repetition was selected for analysis (Eisner, Blanc, et al., 2008). Predicted values were calculated trough a predictive equation (Bohannon, 1997). This measure has a good reliability [ICC=0.87; calculated according to model 2.1 (Shrout & Fleiss, 1979)] and it can be suitably applied for characterising and monitoring changes in people with COPD (O'Shea et al., 2007) and in a clinical setting (Stark et al., 2011).

Handgrip strength, which is a reliable indicator of peripheral muscle strength (Cortopassi, Divo, Pinto-Plata, & Celli, 2011), was measured with a hydraulic hand dynamometer (Baseline Lite Hydraulic Hand Dynamometer, White Plains, NY, U.S.A.), in kilograms (kg). Patients were in the sitting position, with the elbow against the side and flexed in a 90 degrees angle and wrist in a neutral position. The dynamometer was lightly supported. Patients were asked to squeeze the handle of the dynamometer as strongly as they could for about 3 seconds (Spruit, Sillen, Groenen, Wouters, & Franssen, 2013). Three measurements were made from the patients' dominant hand, and the highest value was considered for analysis (Martinez et al., 2017). Normative data (Mendes et al., 2017) was used to calculate percentage of predictive value for each patient. Handgrip measurement in patients with COPD can predict frailty, along with the 6MWT distance, number of exacerbations and comorbidities (Gale et al., 2018). Peripheral muscle strength has been shown to be reduced in patients with COPD (Felipe, Bartolome, Miguel, & Victor, 2015), while lower handgrip values are significantly associated with higher exacerbation frequency (Martinez et al., 2017). This measurement is also strongly associated (z=0.84, 95% CI 0.72-1.00; p=0.04) with mortality in this population (Milo A. Puhan, Siebeling, Zoller, Muggensturm, & ter Riet, 2013).

Respiratory (inspiratory and expiratory) muscles strength was evaluated through the maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) (ATS & ERS, 2002). The respiratory muscle strength was measured with a respiratory pressure meter (MicroRPM, CareFusion, UK). Patients were in the sitting position and the manoeuvres were explained prior to the test. Verbal encouragement was giving during the test. To measure MIP, patients were asked to exhale slowly and completely, then inspire with maximum possible effort and advised to keep it for nearly 1.5 seconds. To measure MEP, patients were instructed to inspire slowly and completely, then expire forcefully with maximum effort for nearly 1.5 seconds. In both tests, patients were instructed to hold the mouthpiece tightly around the lips, to prevent leaks (ATS & ERS, 2002; Vimal, Kolek, & Jaskova, 2012). The maximum value of three manoeuvres which varied by less than 20% was considered (ATS & ERS, 2002). Normative data (ATS & ERS, 2002) was used to calculate percentage of predictive value for each patient. In patients with COPD a decrease in respiratory muscle strength is associated with decreased exercise capacity (Khalil, Wagih, & Mahmoud, 2014; Singer et al., 2011) with a highly significant positive correlation with the 6MWT distance (r=0.546, p=0.0001 and r=0.523, p=0.001, for MIP and MEP, respectively) (Khalil et al., 2014). Moreover, MIP and MEP have shown to be significantly and negatively correlated with mMRC scale (r=-0.954, p=0.0001 and r=-0.905, p=0.0001, respectively) (Khalil et al., 2014). In patients

hospitalised with AECOPD, the respiratory muscles are affected (Mesquita, Donaria, Genz, Pitta, & Probst, 2013; Vimal et al., 2012), nevertheless MIP and MEP were shown to increase after 1 month of hospital discharge, without any specific respiratory muscle strength training (Mesquita et al., 2013).

Lower extremity function was measured with the Short Physical Performance Battery (SPPB) (Puthoff, 2008). The SPPB includes three performance measures, i.e., balance, gait speed and chair stand tests. The balance tests request the maintaining of three standing positions for 10 seconds each: feet side-by-side, semi-tandem stand (i.e., heel of one foot next to the big toe of the other foot) and tandem stand (i.e., heel of one foot directly in front of the other foot). Each position was demonstrated to the patient before the measurement. The maximum score of 4 was given if the patient was capable to maintain the three positions for 10 seconds each; a minimum score of 0 is assigned when the patient was not capable to maintain the side-by-side position for 10 seconds, not progressing to the next position (Bernabeu-Mora et al., 2015; Eisner, Iribarren, et al., 2008; Guralnik et al., 2000; Guralnik, Ferrucci, Simonsick, Salive, & Wallace, 1995; Guralnik et al., 1994; Puthoff, 2008). The gait speed test requires patients to walk 4 meters at their normal pace. The walk was performed two times and the best of the two was considered. The scores were assigned from 0 to 4 according to the time needed to perform the test: 0 if patient was unable to do the walk; 1 if time were more than 8.7 seconds; 2 if time was between 6.21 and 8.7 seconds; 3 if time was 4.82 to 6.2 seconds; and 4 if time was less than 4.82 seconds (Bernabeu-Mora et al., 2015; Eisner, Iribarren, et al., 2008; Puthoff, 2008). The chair stand test measures the time required for the patient to stand up and sit down from a chair five times with his/her arms folded across the chest. Scores ranged from 0 to 4: 0 if the patient was unable to complete the 5-times sit to stand or complete it in more than 60 seconds; 1 if time was more or equal to 16.7 seconds; 2 if time was between 13.7 and 16.69 seconds; 3 if time was between 11.2 to 13.69 seconds; and 4 if time was equal or less than 11.19 seconds. The total score of the SPPB is the sum of the three performance measures, ranging from 0 to 12 (Bernabeu-Mora et al., 2015; Eisner, Iribarren, et al., 2008; Guralnik et al., 2000; Guralnik et al., 1995; Guralnik et al., 1994; Puthoff, 2008). Patients with total scores between 0-3 were classified as having severe limitations, between 4-6 as having moderate limitations, 7-9 as having mild limitations and between 10-12 as having minimal limitations (Puthoff, 2008). The SPPB is a standardised, objective, rapid and simple to conduct test, commonly used in patients with COPD (Bernabeu-Mora et al., 2015; Eisner, Iribarren, et al., 2008). It has shown to have excellent interobserver reliability, test-retest reliability and predictive validity (Freire, Guerra, Alvarado, Guralnik, & Zunzunegui, 2012; Guralnik

et al., 2000; Guralnik et al., 1995; Guralnik et al., 1994). Lower FEV_1 in patients with COPD has been associated with a greater risk of poor lower extremity function (i.e., lower SPPB score) (per 1-liter decrement in FEV_1: odds ratio 1.5, 95% CI 1.2-1.9, p=0.0003) (Eisner, Iribarren, et al., 2008). The SPPB total score is significantly related to the capacity to perform physical activities that are important in daily living, such as changing and maintaining body position, carrying, moving, and handling objects, or walking, being a valid tool to assess mobility limitations in patients with COPD (Bernabeu-Mora et al., 2015). The MCID for SPPB total score has been established as a variation from 0.54-1.34 points (Perera, Mody, Woodman, & Studenski, 2006; Puthoff, 2008). The SPPB chair stand test is equal to the 5-times sit-to-stand test, and this last one has the MCID established as a variation of 1.7 seconds for patients with stable COPD after PR (S. E. Jones et al., 2013). There is no MCID for this test established for AECOPD.

The 1-minute sit to stand test (1'STST) was used to evaluate exercise capacity. The 1'STST was performed in a chair without arms rest. The test was first demonstrated to the patient. Patients were asked to put their hands in their hips without using them for support while rising and sitting, and to complete the sitting and standing positions as correctly, fully and as many times as possible for 1 minute. Patients were permitted to use rest periods to complete the test. The number of completed repetitions was recorded (Meriem et al., 2015; Ozalevli, Ozden, Itil, & Akkoclu, 2007). The 1'STST is strongly correlated with the 6MWT in patients with COPD (r=0.75, p<0.001) (Ozalevli et al., 2007), being less time consuming (Kocks, Asijee, Tsiligianni, Kerstjens, & van der Molen, 2011; Meriem et al., 2015) and producing less hemodynamical stress compared to the 6MWT (Meriem et al., 2015; Ozalevli et al., 2007). It has shown to be sensitive in measuring the efficiency of PR in patients with COPD (Vaidya et al., 2016). The MCID has been established as a variation of 3 repetitions (Vaidya et al., 2016).

All measures were performed at baseline and repeated at patients' discharge by an experienced physiotherapist in a standardised way, using standardised case report forms.

2.5. INTERVENTION

After the baseline assessment, patients initiated the PR programme with an experienced physiotherapist from the hospital.

2.5.1. PULMONARY REHABILITATION PROGRAMME

The PR programme used in this study was adapted to the needs of hospitalised patients from a protocol of PR for patients with lower respiratory tract infections (Marques, Oliveira, & Oliveira, 2016). The protocol consists of three components: techniques for breathing retraining and airway clearance, exercise training and psychoeducational support. A detailed description of the PR programme can be found in Table 1.

Techniques for breathing retraining and airway clearance involved pursed-lips breathing plus Acapella® with apnoea for 3-5 seconds, when possible, during 5-8 cycles (for breathing control and consequent reduction of work of breathing) (He et al., 2015; Valenza et al., 2014), active cycle of breathing techniques (ACBT), exercise with inspiratory controlled flow (EDIC), total slow expiration with glottis open in lateral posture (ELTGOL), with Acapella® in all of the techniques. These techniques were only applied if needed and based on pulmonary auscultation findings in each patient in each session.

Exercise training component included 4 types of exercise: i) thoracic mobility and expansion, and lower limbs mobility exercises (flexion and abduction of the upper limbs, proprioceptive neuromuscular facilitation (PNF) diagonals for upper limbs and extension of the knees), with progression to muscle strengthening with resistance; ii) functional exercises through transfer training between lying, sitting and standing positions; iii) aerobic training by walking; and iv) flexibility training by stretching the muscle groups exercised in each session.

Exercise training was prescribed via Karvonen formula (Karvonen & Vuorimaa, 1988) at a moderate intensity of 40-60% of patients' maximum estimated HR (American College of Sports Medicine, 2014; Goldberg, Elliot, & Kuehl, 1988), and progression was performed individually (Greening et al., 2014; Martin-Salvador et al., 2016), according to patients' HR and dyspnoea levels measured with mBorg scale, where the aim was scores of 3-5 (moderate to severe) (He et al., 2015; Murphy et al., 2005). All patients were monitored during the sessions based on their HR, SpO_2 and mBorg for dyspnoea and fatigue (Jenkins, Hill, & Cecins, 2010; Spruit, Singh, et al., 2013). Delaying exercise training was considered for patients with an abnormal resting HR (i.e. <50 or ≥125 bpm), SpO_2<90% or excessive dyspnoea at rest (scores on the mBorg≥4) (Jenkins et al., 2010).

Expansion and thoracic mobility exercises were performed in the most vertical position tolerated by each patient (lying down with a headboard elevated, sitting or standing position), and from the number of repetitions that the patient could performed due to his/her perceived fatigue and dyspnoea (Torres-Sanchez et al., 2016). The objective was

to perform 2 sets of 10 repetitions of each exercise (Martin-Salvador et al., 2016). When the patient was able to achieve the objective with a dyspnoea level between 3-5 in the modified Borg scale (He et al., 2015; Murphy et al., 2005), the exercises began to be performed with a TheraBand® to confer an elastic resistance of low-impact (Borges & Carvalho, 2014; Murphy et al., 2005) with the produced force depending on the percentage of stretch of the TheraBand® (Murphy et al., 2005).

Aerobic training consisted of walking in the corridor, with a dyspnoea level of 3-5 on the mBorg determining the speed and duration of walking (He et al., 2015; Murphy et al., 2005). This exercise was initiated when the patient could initiate walking. In the first walk, the time that the patient could maintain a 3-5 dyspnoea level in the mBorg (He et al., 2015; Murphy et al., 2005) was noted, representing the initial training time (Torres-Sanchez et al., 2017). In the following days the objective was to increase the time until the patient was able to perform 10 minutes of sustained walking.

The psychoeducational support included the teaching of breathing control and positions for relaxation and dyspnoea relief during the sessions, and the delivery of flyers from the PR protocol for patients with lower respiratory tract infections (Marques et al., 2016) through the sessions. The flyers contained information about breathing control and positions for dyspnoea relief (flyers 1 and 2, delivered in first session), airway clearance techniques (flyer 3, delivered in second session), lower respiratory tract infections (flyer 4 part 2, delivered in third session) and exercise (flyer 5, delivered in the last session).

In the flexibility training, each stretching position was initially maintained for 10 seconds, continuously progressing to 30 seconds (American College of Sports Medicine, 2014).

Table 1 – Pulmonary rehabilitation programme for patients hospitalised with acute exacerbation of chronic obstructive pulmonary disease (AECOPD)

Component	Techniques	Goal/Progression	Monitoring
Breathing retraining and airway clearance*	Pursed-lips breathing plus Acapella® (apnoea for 3-5s, 5-8 cycles) ACBT (3-5 repetitions) EDIC and/or ELTGOL plus Acapella® (apnoea 3-5s, 10 repetitions)		
Exercise training	Flexion of the upper limbs Abduction of the upper limbs PNF diagonals for upper limbs Extension of the knees	First: 2 sets of 10 repetitions Second: muscle strengthening training with a TheraBand®	mBorg dyspnoea level: 3-5 SpO_2 > 90% HR: 40-60% of maximum estimated HR
	Functional exercises	Transfer training from bed to chair Transfer training from chair to stand	
	Aerobic training: walking	10 minutes of continuous walk	
	Flexibility training: stretching the muscle groups exercised in each session	Each stretching position was initially maintained for 10 seconds, continuously progressing to 30 seconds	

Psychoeducational support	Education on breathing control and positions for relaxation and dyspnoea relief during the sessions	
	Delivery of some flyers through the sessions	Session 1: breathing control and positions for dyspnoea relief
		Session 2: airway clearance techniques
		Session 3: lower respiratory tract infections
		Last session: Exercise

Adapted from Marques, A., Oliveira, A., & Oliveira, D. (2016). Gerir a infeção respiratória do trato inferior na comunidade: o papel do fisioterapeuta. Lisbon: Lusodidacta.

*Only applied if needed and based on pulmonary auscultation findings.

Legend: ACBT, Active cycle of breathing techniques; EDIC, exercise with inspiratory controlled flow; ELTGOL, total slow expiration with glottis open in lateral posture; HR, heart rate; mBorg, modified Borg scale; PNF, proprioceptive neuromuscular facilitation; SpO_2, peripheral oxygen saturation.

The duration of each session ranged from 20-60 minutes, 5 days a week. The organisation and duration of each component of the PR programme in each session depended of the individual and daily evaluation. Heart rate, SpO_2 and mBorg scale for dyspnoea levels were collected at the beginning and at the end of each session (Jenkins et al., 2010). Sessions occurred in the ward or in the physical and rehabilitation medicine service, depending on the daily evaluation, the will of each patient and according to the convenience of the service. Any adverse event occurring during the sessions [i.e., dyspnoea and/or fatigue levels of 7 or more in the mBorg, vertigo, syncope, cyanosis (Borges & Carvalho, 2014), pain, sweating (Torres-Sanchez et al., 2017; Torres-Sanchez et al., 2016), and/or falls (Tang et al., 2012)] was recorded and the session was ended, followed by hospital procedures. If SpO_2 dropped below 88%, oxygen was administered (Borges & Carvalho, 2014; He et al., 2015; Nava, 1998; Tang et al., 2012; Torres-Sanchez et al., 2017) if there was medical indication, and the exercise was stopped until the patient recovered.

2.1. Three-Months Follow-Up

Three months after hospital discharge, the electronic clinical process of each patient was consulted to verify any visits to the emergency service or another hospitalisation. The number and the motive of each event was recorded.

2.2. Data Analysis

Data were analysed using IBM SPSS Statistics version 24.0 (IBM Corporation, Armonk, New York, USA) and plots were created using the Microsoft Excel® (Microsoft® Office 365®, Microsoft Windows® 10 Home).

Descriptive statistics were applied to characterise the sample (i.e., sociodemographic, anthropometric and general clinical data, PA levels and cardiorespiratory parameters) and to analyse the follow-up data. The normality of the data was explored with the Shapiro-Wilk tests. All comparisons between baseline and discharge assessments were performed with Wilcoxon signed-rank tests. The level of significance considered was set at $p<0.05$.

Effect sizes (ES) were calculated as the repeated measures ES, since this study had a single-group pretest–posttest design (Morris & DeShon, 2002). Effect sizes were interpreted as small (≥0.2), medium (≥0.5) or large (≥0.8) (Cohen, 1988). Whenever possible, the number and percentage of patients that improved above the MCID was determined.

3. RESULTS

A total of twenty-six hospitalised patients with AECOPD were referred for possible inclusion in the study. From these, one patient refused to participate and ten were excluded due to the following reasons: incapacity to complete the assessment (n=1), presence of a pulmonary nodule (n=2), active neoplasia (n=2), need of non-invasive mechanical ventilation 24 hours per day (n=2) and discharge immediately after reference from the physician (n=3). Thus, 15 patients were included in the study and completed the baseline assessment. All 15 patients completed the PR programme during hospitalisation, however only 10 were assessed at discharge due to time constraints in scheduling the reassessment. Figure 1 shows the flow chart of the sample recruitment.

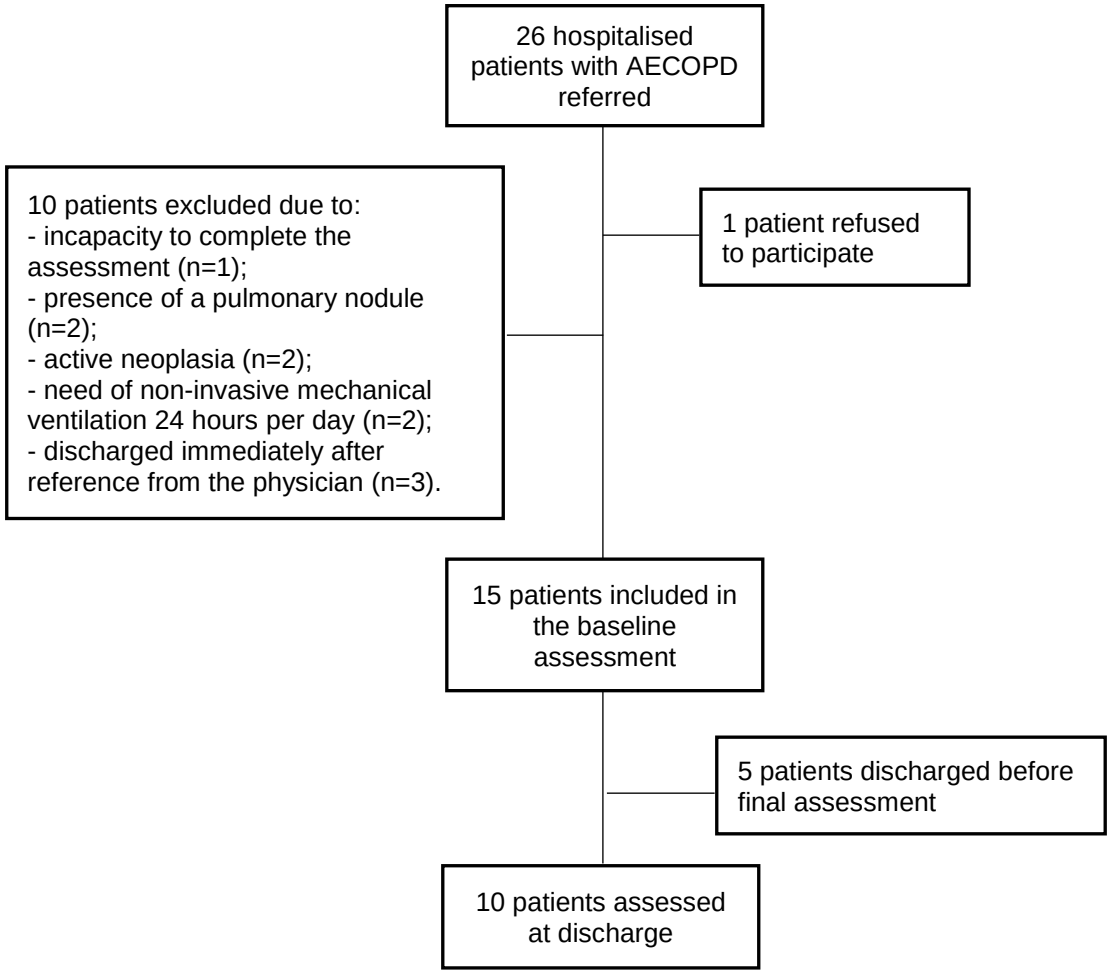

Figure 1 – Flow chart of the recruitment of hospitalised patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) to participate in the study.

3.1. PATIENTS' CHARACTERISATION

Sociodemographic characteristics of the 15 hospitalised patients with AECOPD evaluated at baseline are shown in Table 2. Patients were mostly male (n=14; 93.3%), had a mean age of 71.2±7.2 years old, 4 years of education (n=9; 60%), were married (n= 9; 60%) and retired (n=15; 100%).

Table 2 – Sociodemographic characteristics of the hospitalised patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) included in the study (n=15).

Characteristics	Patients (n=15)
Gender, n (%)	
Male	14 (93.3)
Female	1 (6.7)
Age, years	71.2±7.2
Education, n (%)	
<1 year	3 (20)
1-4 years	9 (60)
7-9 years	1 (6.7)
10-12 years	1 (6.7)
>13 years	1 (6.7)
Marital Status, n (%)	
Married	9 (60)
Divorced	3 (20)
Widowed	3 (20)
Occupation, n (%)	
Retired	15 (100)

Data are presented as mean±standard deviation or number of patients (percentage of patients), unless otherwise stated.

Patients were mostly overweight (BMI=25.2±4.5Kg/m^2), former smokers (n=8; 53.3%) with a median of 37 [19.4; 48.5] pack-years, presented severe airflow obstruction (n=7; 46.7%; 46.1±20.6 FEV_1%predicted) according to the international guidelines (The Global Initiative for Chronic Obstructive Lung Disease, 2018) [one patient was unable to perform acceptable spirometry according to the international guidelines (Miller et al., 2005)] and were classified as GOLD D (n=9; 60%). Six patients (40%) used long-term oxygen therapy and 4 (26.7%) used non-invasive ventilation. According to the CCI, 8 patients (53.3%) had moderate and 7 (46.7%) had severe comorbidities, and according to the brief-PA tool 11 patients (73.3%)

were insufficiently active. Although a combination of medication was prescribed, most patients were taking antibiotics (n=11; 73.3%). Patients were hospitalised for 7 to 24 days (mean 13±4.3 days) and received 2 to 8 sessions of PR (mean 4.7±2 sessions). Patients' detailed clinical characterisation is summarised in Table 3.

Table 3 - Clinical characterisation of the hospitalised patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) included in the study (n=15).

Characteristics	Patients (n=15)
BMI, kg/m^2	25.2±4.5
Smoking status, n (%)	
Current	3 (20)
Former	8 (53.3)
Never	4 (26.7)
Packs/year	37 [19.4; 48.5]
Exacerbations/year	2 [1; 3.25]
Hospitalisations/year	1 [0; 2]
Visits to the emergency service/year	1 [1; 3]
FEV_1, L	1.2±0.6
FEV_1, %predicted	46.1±20.6
FVC, L	2.4±0.6
FVC, predicted	78.9±30
FEV_1/FVC, %	48.6±14.8
mMRC	3 [2; 4]
GOLD grade, n (%)	
1	2 (13.3)
2	3 (20)
3	7 (46.7)
4	2 (13.3)
GOLD groups, n (%)	
A	0 (0)
B	3 (20)
C	2 (13.3)
D	9 (60)
Comorbidities (CCI), n (%)	
Mild	0 (0)

Moderate	8 (53.3)
Severe	7 (46.7)
Medication use, n (%)	
Antibiotics	11 (73.3)
Expectorants	3 (20)
ICS	3 (20)
ICS+LABA	6 (40)
LABA	2 (13.3)
LAMA	4 (26.7)
LAMA+LABA	5 (33.3)
LTRA	1 (6.7)
SABA	5 (33.3)
SAMA	1 (6.7)
Xanthines	5 (33.3)
Long-term oxygen therapy, n (%)	6 (40.0)
Non-invasive ventilation, n (%)	4 (26.7)
Brief-PA, n (%)	
"Sufficiently" active	4 (26.7)
"Insufficiently" active	11 (73.3)
Number of days hospitalised	13±4.3
Number of pulmonary rehabilitation sessions	4.7±2

Data are presented as mean±standard deviation or median [interquartile range], unless otherwise stated.

Legend: Brief-PA, Brief Physical Activity Assessment Tool; BMI, body mass index; CCI, Charlson Comorbidity Index; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled corticosteroids; LABA, Long-acting beta-2 agonists; LAMA, Long-acting muscarinic antagonist (anticholinergic); LTRA, Leukotriene Receptor Antagonists; mMRC, modified Medical Research Council dyspnoea questionnaire; SABA, Short-acting beta-2 agonists; SAMA, Short-acting muscarinic antagonist (also called short-acting anticholinergic).

3.2. EFFECTS OF THE PULMONARY REHABILITATION PROGRAMME

There were no significant differences between the 10 patients who completed the 2 assessments and the 5 patients who only completed the baseline assessment in terms of age, gender, BMI, GOLD groups and FEV_1 ($p>0.05$). Baseline and discharge assessments results are shown in Table 4. After discharge, significant improvements were found in dyspnoea assessed with the mBorg scale (Baseline 3 [2; 4] vs. Discharge 2 [0; 3], p=0.008),

systolic and diastolic BP (Baseline 127 [118; 139] vs. Discharge 112 [107.8; 119.5], p=0.016; Baseline 79 [67; 87] vs. Discharge 64 [53.8; 77.3], p=0.008, respectively) and the CAT (Baseline 20 [17; 27] vs. Discharge 17 [8.8; 23.5], p=0.01). No significant differences were found in the remaining outcome measures (Table 4) however, plotting the data for each variable (Figure 2), it was observed that almost every outcome measure improved in at least 50% of the sample.

Systolic and diastolic BP, dyspnoea assessed with the mBorg scale, and the CAT presented large effects (ES=-1.584; ES=-1.231; ES=-0.976; ES=-0.925, respectively). Medium effects were found in the mMRC (ES=-0.702), fatigue, assessed with the mBorg scale, (ES=-0.546) and QMS (ES=0.662). The remaining outcome measures presented small effects (i.e., from 0.048 in handgrip %predicted to 0.443 in SPPB total score) (Table 4). No adverse events were reported.

Table 4 - Descriptive and inferential statistics before and after the hospitalised pulmonary rehabilitation programme in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

	Baseline (n=15)	**Discharge (n=10)**	**p-value**	**ES**
mMRC grade	3 [2; 4]	2 [1; 3]	0.172	-0.702
HR (bpm)	82 [75; 97]	74.5 [64.3; 84.3]	0.441	-0.261
RR (cpm)	20 [20; 20]	20 [19; 20]	0.531	-0.437
SpO_2 (%)	95 [92.8; 97.3]	94 [92; 95.3]	1	-0.058
Systolic BP (mmHg)	127 [118; 139]	112 [107.8; 119.5]	0.016*	-1.584
Diastolic BP (mmHg)	79 [67; 87]	64 [53.8; 77.3]	0.008*	-1.231
Dyspnoea (mBorg)	3 [2; 4]	2 [0; 3]	0.008*	-0.976
Fatigue (mBorg)	3.5 [1.8; 4.3]	2.5 [0; 4]	0.344	-0.546
CAT total score	20 [17; 27]	17 [8.8; 23.5]	0.01*	-0.925
FEV_1, L	1 [0.9; 1.6]	1.1 [0.7; 1.9]	0.367	0.247
FEV_1, %predicted	40 [32.5; 62.9]	42 [28.5; 76.5]	0.313	0.280
FVC, L	2.3 [1.7; 3]	2.5 [2.3; 3]	0.625	0.279
FVC, %predicted	76 [59.5; 91]	74 [68; 93.5]	0.477	0.319

FEV_1/FVC, %	45.4 [36.8; 61]	45 [38; 64.5]	0.258	0.133
QMS (kgf)	21.2 [18.7; 23.4]	25.3 [22.9; 27.2]	0.24	0.662
QMS, %predicted	62.2 [53.9; 70.8]	68.1 [63.2; 72.9]	0.25	0.496
Handgrip (kg)	28 [24; 30]	29 [26.8; 30.5]	1	0.060
Handgrip, %predicted	85.9 [81.3; 104.5]	91.5 [78.2; 106.6]	1	0.048
MIP (cmH_2O)	62 [44; 71]	70 [55.5; 97.8]	0.266	0.063
MIP, %predicted	59.2 [38.9; 62.8]	61.9 [49.1; 86.1]	0.266	0.063
MEP (cmH_2O)	90 [70.5; 127]	133.5 [88.5; 141.8]	0.469	0.281
MEP, %predicted	58.5 [45.8; 82.5]	86.7 [57.5; 92.1]	0.438	0.281
SPPB total score	9 [8; 11]	11.5 [8; 12]	0.156	0.443
Total Balance Tests score	4 [4; 4]	4 [4; 4]	1	**
Gait speed test score	3 [1; 4]	3.5 [3; 4]	0.531	0.396
Gait speed test (seconds)	5.1 [4.8; 9.6]	4.9 [3.7; 5.5]	0.131	0.279
Chair stand test score	2 [1; 4]	4 [1.8; 4]	0.75	-0.384
Chair stand test (seconds)	14.5 [10.1; 18.2]	10.1 [8.3; 16.8]	0.131	-0.384
1'STST (repetitions)	16.5 [12; 22.3]	16.5 [14; 31.8]	0.053	0.386

Data are presented as median [interquartile range], unless otherwise stated. *p<0.05. **pre and post values are equal.

Legend: 1'STST, 1-minute sit-to-stand test; BP, blood pressure; CAT, COPD assessment test; ES, effect size; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HR, heart rate; mBorg, modified Borg scale; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; mMRC, modified Medical Research Council dyspnoea questionnaire; QMS, quadriceps muscle strength; RR, respiratory rate; SpO_2, peripheral oxygen saturation; SPPB, short physical performance battery.

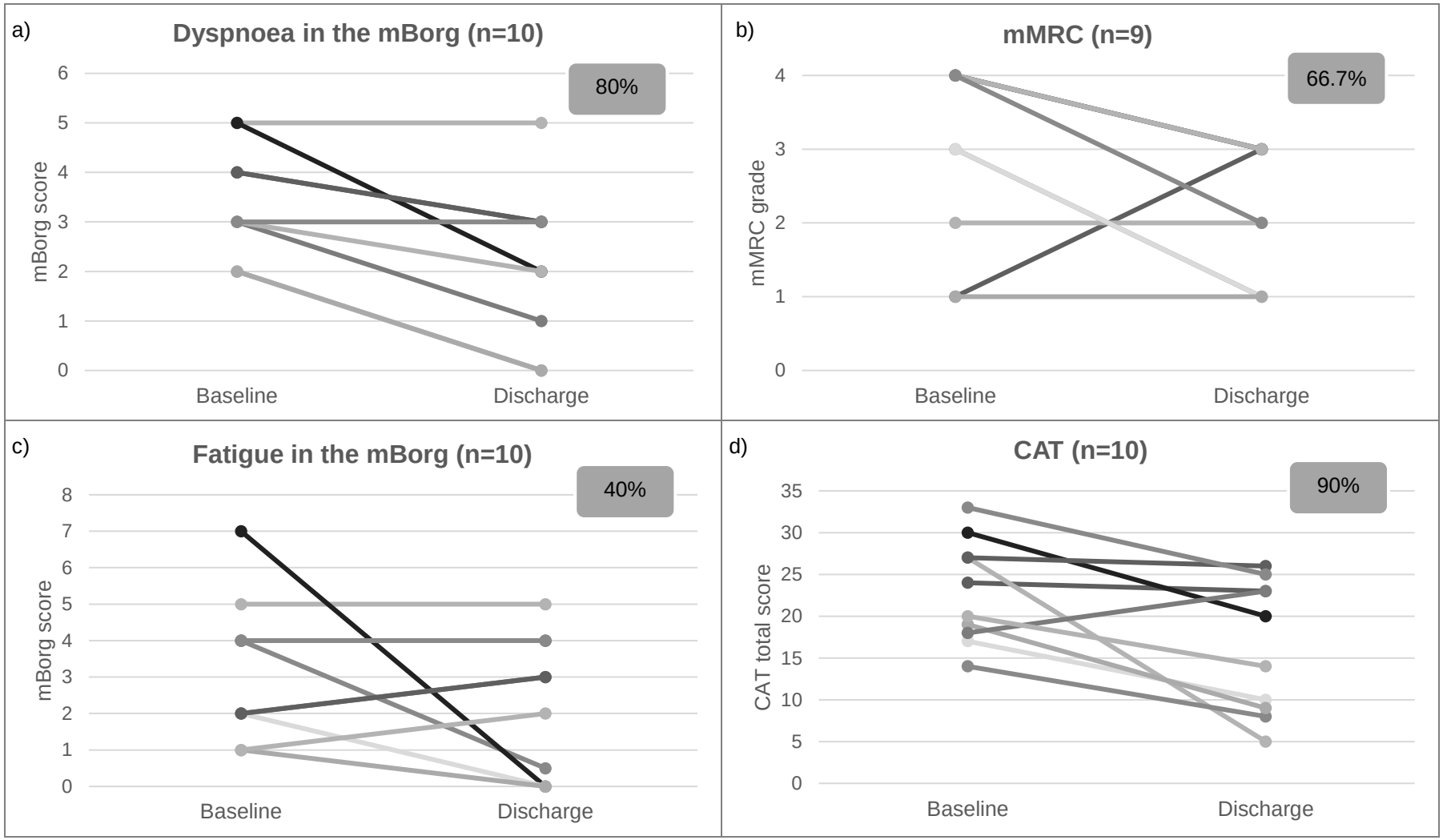

Figure 2 – Comparison between baseline and hospital discharge assessment of each outcome measure per patient: a) dyspnoea in the modified Borg scale (mBorg); b) modified Medical Research Council dyspnoea questionnaire (mMRC); c) fatigue in the mBorg; d) the COPD assessment test (CAT) total score. The number in the upper right corner of each chart indicates the percentage of patients that improved in each measure. [cont.]

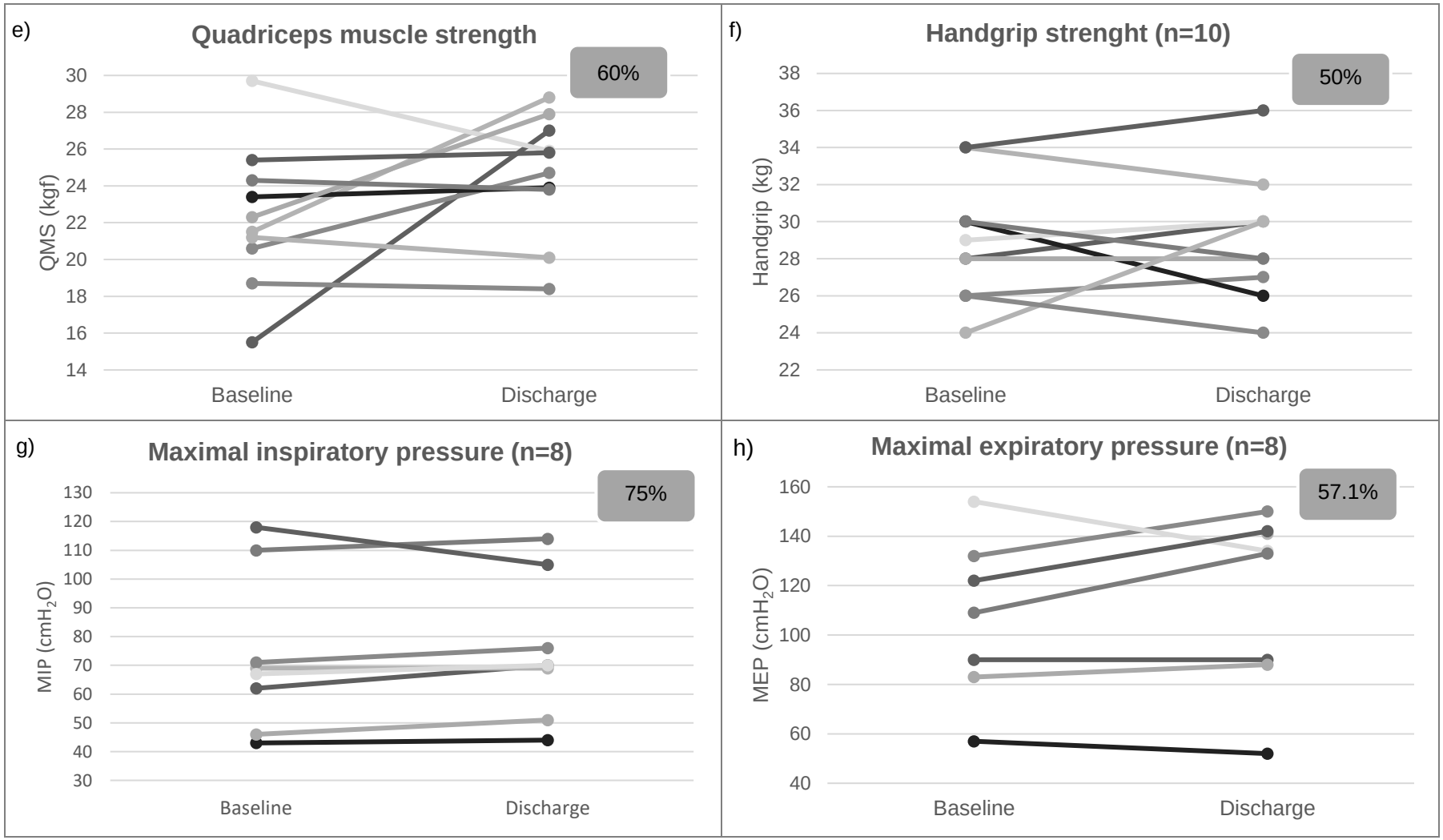

Figure 2 – Comparison between baseline and hospital discharge assessment of each outcome measures per patient: e) quadriceps muscle strength (QMS) in kilogram force (kgf); f) handgrip in kilogram (kg); g) maximal inspiratory pressure (MIP) in cmH_2O; h) maximal expiratory pressure (MEP) in cmH_2O. The number in the upper right corner of each chart indicates the percentage of patients that improved in each measure. [cont.]

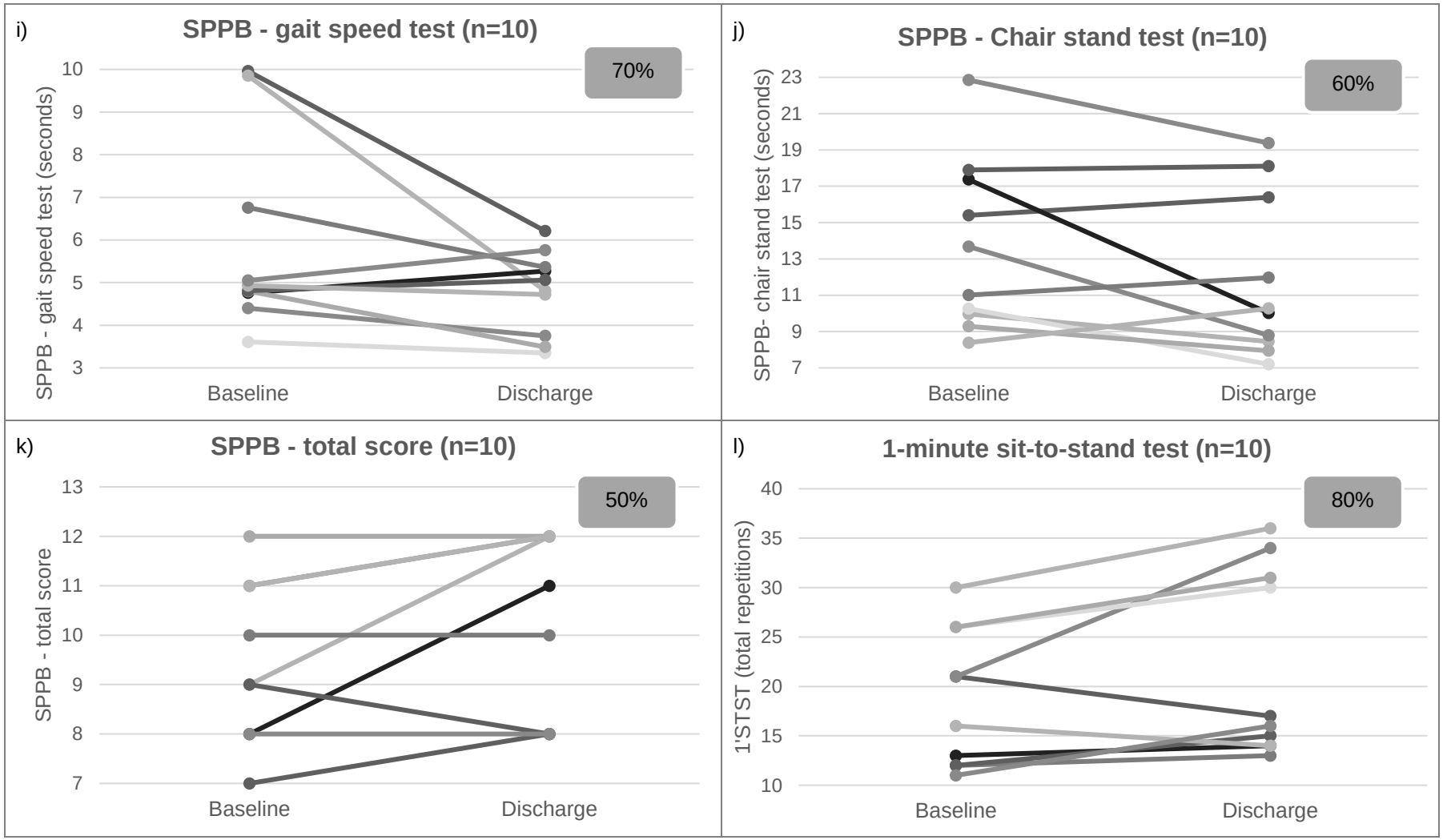

Figure 2 – Comparison between baseline and hospital discharge assessment of each outcome measures per patient: i) Short physical performance battery (SPPB) gait speed test; j) SPPB chair stand test; k) SPPB total score; l) 1-minute sit-to-stand test (1'STST). The number in the upper right corner of each chart indicates the percentage of patients that improved in each measure.

There were 8 (80%) patients improving above the MCID on dyspnoea at rest, assessed with the mBorg, 7 (70%) on the CAT, 6 (60%) on the mMRC, 6 (60%) on the 1'STST, 5 (50%) on SPPB total score and 4 (40%) on the chair stand test of the SPPB (Figure 3).

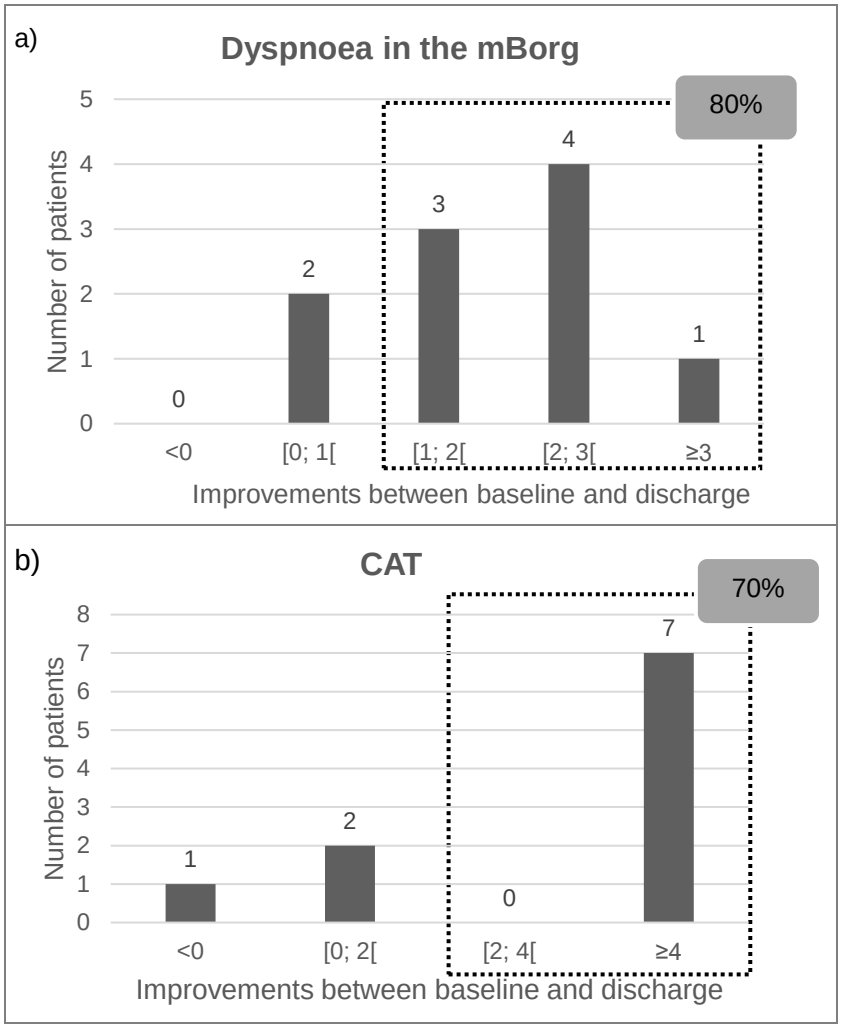

Figure 3 - Distribution of the improvement between baseline and hospital discharge assessment relatively to the minimal clinically important difference (MCID) for each measure: a) symptoms of dyspnoea in the modified Borg scale (mBorg); b) the COPD assessment test (CAT) total score. Dashed line indicates the number of patients that improved above the MCID for each measure, i.e., mBorg – 1 unit, CAT – 2 points. The number in the upper right corner of each chart indicates the percentage of patients that improved in each measure [cont.]

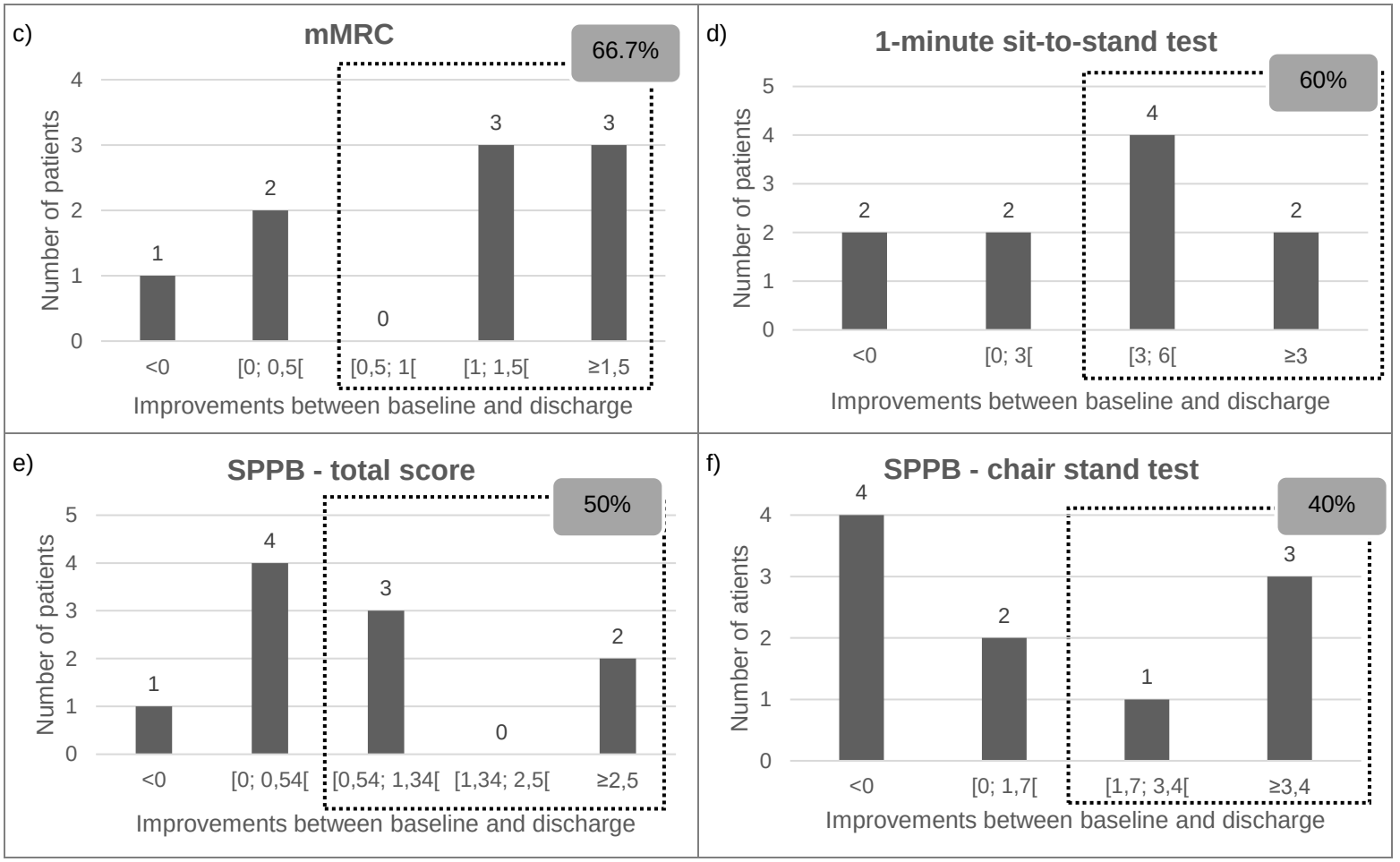

Figure 4 - Distribution of the improvement between baseline and hospital discharge assessment relatively to the minimal clinically important difference (MCID) for each measure: c) the modified Medical Research Council dyspnoea questionnaire (mMRC); d) 1-minute sit-to-stand test (1'STST); e) short physical performance battery (SPPB) total score; f) SPPB chair stand test. Dashed line indicates the number of patients that improved above the MCID for each measure, i.e., mMRC – 0.5 units, 1'STST – 3 repetitions, SPPB – 0,54-1,34 points, SPPB chair stand test – 1,7s. The number in the upper right corner of each chart indicates the percentage of patients that improved in each measure.

3.1. FOLLOW-UP OF 3 MONTHS

Three months after hospital discharge, 6 (40%) patients visited the emergency service in a total of 10 visits (i.e., 3 patients visited the emergency service once, 2 patients visited twice and 1 visited 3 times) due to dyspnoea (8 times – 80%), fever (1 time – 10%) and thoracic pain (1 time – 10%). From these 6 patients, 4 (26.7%) were hospitalised, in a total of 9 hospitalisations (i.e., 3 patients were hospitalised 2 times and 1 patient 3 times), with a mean of 11.8±5.7 days of hospitalisation. Eight of these 9 hospitalisations were due to new AECOPD and the other was not respiratory related (Table 5).

Table 5 – Follow-up of 3 months after hospital discharge of patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) (n=10).

	Patients (n=15)
Visits to the emergency service	
Number of patients, n (%)	6 (40)
Number of visits, n	10
Motive for visit emergency service, n (%)	
Dyspnoea	8 (80)
Fever	1 (10)
Thoracic pain	1 (10)
Hospitalisation	
Number of patients, n (%)	4 (26.7)
Number of Hospitalisations, n	9
Motive for hospitalisation, n (%)	
AECOPD	8 (88.9)
Not respiratory related	1 (11.1)

Data are presented as number of patients (percentage of patients), unless otherwise stated.
Legend: AECOPD, acute exacerbations of chronic obstructive pulmonary disease.

4. DISCUSSION

This pilot study showed that PR in hospitalised patients with AECOPD is safe and effective. Significant improvements were found on dyspnoea at rest, BP and impact of the disease. Although, controversy has been installed with some authors recommending (Spruit et al., 2018) and others not recommending (Jadwiga A. Wedzicha, Miravitlles, et al., 2017) PR during hospitalisations, similar benefits (i.e., with significant improvements in SpO_2, dyspnoea, impact of the disease and exercise capacity), have been reported in another study conducted in hospitalised patients between the second day of admission

until discharge (He et al., 2015). Moreover, significant improvements in RR, SpO_2, dyspnoea at rest, QMS and impact of the disease (Machado, 2018) have also been demonstrated in patients with AECOPD after a community-based PR programme of 3 weeks.

Dyspnoea at rest, assessed with the mBorg scale, improved significantly, but not when assessed with the mMRC. This was an expected result as mMRC has been reported to lack sensitivity to capture relevant changes in breathlessness following an intervention (Bausewein et al., 2007), despite having a strong discriminative value (Spruit, Singh, et al., 2013). Another important domain that did not improve significantly was the fatigue at rest. Associations between reduced time spent outdoors and increased fatigue have been shown and may explain our results, as hospitalised patients are often confined to indoor areas (Baghai-Ravary et al., 2009). Fatigue is a highly prevalent and incapacitating symptom in patients with COPD, that affects social participation and increases the burden of the disease (Spruit, Vercoulen, Sprangers, & Wouters, 2017), however it is often undervalued by health professionals. Our findings show that fatigue is also highly prevalent [8 (53.3%) patients indicated fatigue above 3 (moderate) in de mBorg scale at rest at baseline] in patients with AECOPD, with an intensity similar to dyspnoea, measured by the mBorg, and although significant results were not observed, approximately 40% of our patients improved in fatigue at rest (medium effect size). Similar to other PR programmes conducted in hospitalised patients (He et al., 2015; Liao et al., 2015; Martin-Salvador et al., 2016; Tang et al., 2012), fatigue was not targeted specifically, but our findings demonstrate that strategies to manage fatigue need to be included in PR programmes conducted in this population.

Blood pressure, both systolic and diastolic, demonstrated significant improvements in this study, with the largest effects observed. No studies were found which correlated BP and hospitalised patients with AECOPD undergoing a PR programme, however one study (Canavan et al., 2015) demonstrated that community-based PR in patients with stable COPD is unlikely to reduce BP. It is known that hospitalised patients with AECOPD suffer from anxiety and depression (Valenza et al., 2014), and these symptoms appear to increase BP (Edmondson, Arndt, Alcantara, Chaplin, & Schwartz, 2015). At discharge it is likely that patients were less anxious as their symptoms have improved and they were ready to leave the hospital, thus lowering their BP and justifying the significant improvement observed. More studies investigating the role of PR in BP changes and the association among anxiety (and other possible factors), hospitalisation, and BP are required to better understand these results. Contrary to BP and to previous

studies (Ali et al., 2014; He et al., 2015; Machado, 2018), SpO_2 did not demonstrate significant improvements, possibly due to the fact that at baseline assessment 9 patients were using supplementary oxygen, probably because these patients presented hypoxaemia and needed supplementary oxygen to achieve an SpO_2 target of 88–92% (Pilcher, Weatherall, Perrin, & Beasley, 2015). However at discharge only 3 patients maintained supplementary oxygen, which could mean that the majority of patients improved and did not needed supplementary oxygen to maintain the SpO_2 target. Notwithstanding, more studies are needed to understand the role of PR in the SpO_2 in patients with and without supplementary oxygen.

Impact of the disease demonstrated significant improvements. There are few studies applying the CAT in patients with AECOPD undergoing PR programmes, nevertheless studies that used CAT did found significant improvements after PR (He et al., 2015; Machado, 2018). Most studies on PR in AECOPD have used the SGRQ to assess health-related quality of life (A. L. Oliveira & Marques, 2018) and thus comparisons are difficult to establish. However, the routine use of SGRQ during hospitalisation is arguable as questions report to the past month, 3 months and 1 year (A. L. Oliveira & Marques, 2018), when commonly patients with AECOPD present only a few days of hospitalisation (in this study the mean was of 13 days). The CAT has been showing good measurement properties (P. W. Jones et al., 2009) to be used in patients with AECOPD and is similar to SGRQ in terms of discriminating health status (Morishita-Katsu et al., 2016), thus it may be an emerging outcome measure to be used in hospitalised patients. Due to its previous good results and simpleness to be implemented, future studies should further explore and validate CAT in this setting.

No improvements were found on quadriceps and respiratory muscle strength. QMS weakness is often presented in patients with COPD, and it is known to become worse during hospitalisation in patients with AECOPD (Spruit et al., 2003). This study did not find significant improvements in QMS, however 60% of patients increased QMS (medium effect size) which would have been unlikely to happen if patients were not undertaking PR since it has been demonstrated that hospitalisation weakens the peripheral muscles due to the higher immobilisation period (Martin-Salvador et al., 2016; Spruit et al., 2003). More studies with larger samples are required to clarify the role of PR in preventing the usual degradation of peripheral muscle strength during hospitalisations for AECOPD. Regarding to respiratory muscle strength, studies in stable patients with COPD and without a specific respiratory muscle training component have demonstrated mixed results on the effects of PR, in respiratory muscle strength (Charususin et al., 2018; van

Wetering, Hoogendoorn, Mol, Rutten-van Molken, & Schols, 2010). In the present study, most patients did not have respiratory muscle weakness and therefore, a specific respiratory muscle training component was not included. Inclusion of respiratory muscle training during PR should however be considered in programmes conducted in any setting, including in hospitalised patients with AECOPD, when respiratory muscle weakness is present (Nici et al.).

Patient's lower extremity function, measured with the SPPB, did not improve significantly. SPPB has been commonly used in patients with COPD (Bernabeu-Mora et al., 2015; Eisner, Iribarren, et al., 2008; Medina-Mirapeix et al., 2016; Patel et al., 2014; Volpato et al., 2011), and it has been advocated to be a useful tool for evaluating physical performance in less functioning patients (Larsson, Borge, Nygren-Bonnier, Lerdal, & Edvardsen, 2018), as it presents a ceiling effect in high-functioning patients (Larsson et al., 2018). In the present study, a ceiling effect was only observed in the balance tests of the SPPB, where every patient started in the maximal score. The reliability of the balance component of the SPPB has been questioned (Medina-Mirapeix et al., 2016) and might not be the most adequate test to measure balance in patients with AECOPD. Studies with the purpose of assessing balance in this population should use a more specific and comprehensive measure, such as Balance Evaluation System Test (BESTest) or its shorter versions (Beauchamp, Harrison, Goldstein, & Brooks, 2016; Beauchamp et al., 2013; Jacome, Cruz, Oliveira, & Marques, 2016).

Contrary to what has been previously reported (Clini et al., 2009; He et al., 2015; Nava, 1998), no significant improvements in exercise capacity were found, as assessed with the 1'STST. Changes in 1'STST after PR have shown strong correlations with changes in the 6MWT distance (Ozalevli et al., 2007; Vaidya et al., 2016) but also with changes in QMS (Vaidya et al., 2016), thus reflecting that performance on this test is also dependent of patients' QMS. In this study, only 6 (60%) patients improved in QMS, which may justify the lack of improvements in the 1'STST. Previous studies have used the 6MWT, incremental shuttle walk test (ISWT) and endurance shuttle walk test (ESWT) to assess exercise capacity (A. L. Oliveira & Marques, 2018), however these measures may not be feasible in clinical practice. The 6MWT is a practical simple test, but it requires a quiet 30 meters hallway (American Thoracic Society, 2002), whilst the ISWT (Singh, Morgan, Scott, Walters, & Hardman, 1992) and the ESWT (Revill, Morgan, Singh, Williams, & Hardman, 1999) require a quiet 10 meters hallway, which is difficult to obtain in an hospital ward. Future research should focus on exploring alternative outcome measures to assess exercise capacity in hospital wards.

Three months after discharge, 6 (40%) patients visited the emergency service, and from these, 4 (26.7%) were hospitalised mainly due to relapses of the AECOPD. The 6 patients who needed to use health services in the 3 months after discharge were the ones with a higher value in the CCI, confirming previous literature showing that the number of comorbidities is associated with increased risk of exacerbations and hospitalisation (Almagro et al., 2012; Putcha et al., 2015; Smith & Wrobel, 2014; Soler-Cataluna et al., 2005; The Global Initiative for Chronic Obstructive Lung Disease, 2018). Future research should study a more tailored intervention for patients with high number of comorbidities to prevent the higher risk of exacerbations. In another perspective, this study had 40% of patients returning to health services in 3 months, 26.7% being hospitalised. In another study (Eaton et al., 2009), PR was initiated during the hospitalisation of the patients with AECOPD and continued in the community setting for 8 weeks. This study presented readmission of 11 patients in 47 (23.4%) at 3 months, with a non-significant tendency towards reduced COPD-related readmissions compared to a control group. Considering that 40% of our patients returned to the health services, it becomes clear that it is essential to continue the support of these patients in the community to minimise the need to resort to hospitals.

4.1. Limitations and Future Research

The present study has some limitations that need to be acknowledged. Firstly, a control group was not included, which prevents us from inferring about the effectiveness of the intervention when compared with the current standard of care for AECOPD. Secondly, the period of data collection was long (i.e., between January and August), and yet the number of patients referred was small. Additionally, although 15 patients were initially included, only 10 completed the discharge assessment. This difficulty in recruiting and enrolling patients with AECOPD in non-pharmacological interventions has been demonstrated in another study (Janaudis-Ferreira et al., 2018). Consequently, the results of this study have been based on a small sample size, which limits the strength of our conclusions. Nevertheless, given the potential of the results achieved, a more robust methodology including randomised designs, with larger samples and blind assessors is now essential to clarify the role of PR in hospitalised patients with AECOPD. Thirdly, the number of PR sessions differed among patients (i.e., 2 to 8 sessions), which could influence the individual and overall results. New studies are needed to establish the minimal number of PR sessions required to promote significant improvements. Finally, the long-term effects of the PR programme in hospitalised patients were not

assessed due to the limited time available to conduct this study. Given the long-term consequences of AECOPD on patients' health status and disease progression (Haughney et al., 2005), a careful assessment of the long-term effects of PR during AECOPD is required.

5. CONCLUSIONS

This pilot study demonstrated that PR programmes during patients' hospitalisations due to AECOPD appear to be safe and effective, promoting similar improvements to the already recognised benefits of PR in stable patients with COPD. Implementation of PR in hospitalised patients with AECOPD resulted in significant improvements in dyspnoea, BP, and impact of the disease. Nonetheless, since approximately 40% of the patients required health services within 3 months of follow-up, it becomes clear that support of these patients needs to be continued in the community to minimise the necessity to resort to hospitals. This information might be useful to develop tailored interventions to treat patients with AECOPD that need hospitalisation. Future research with more robust methodologies, randomised controlled studies with larger samples and longer follow-up periods are desirable to confirm these results.

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Appendix A – Information sheets to the patients

Folha de informação ao participante

O Sr./Sra. está a ser convidado/a para participar no estudo de investigação clínica intitulado: "Efeitos da reabilitação respiratória hospitalar nas exacerbações agudas da doença pulmonar obstrutiva crónica". Mas, antes de decidir, é importante que compreenda porque é que a investigação está a ser realizada e o que é que a mesma envolve. Por favor, leia a informação com atenção e discuta a sua participação com outros, se assim o entender. Se houver algo que não esteja claro para si ou necessitar de informação adicional, por favor pergunte aos investigadores (contactos no final deste documento). Use o tempo que precisar para decidir se deseja ou não participar.

Muito obrigado desde já por ler a informação.

Qual é o propósito do estudo?

Este estudo visa determinar o efeito da reabilitação respiratória em utentes hospitalizados por exacerbação aguda da Doença Pulmonar Obstrutiva Crónica (DPOC). Adicionalmente, pretende também caracterizar os utentes com exacerbação aguda da DPOC, avaliar a sua evolução durante a hospitalização (i.e., sintomas e o seu impacto, função pulmonar, funcionalidade e força muscular)ca e o seu prognóstico (i.e., tempo de internamento e re-hospitalizações até aos 3 meses).

Para que seja possível alcançar estes objetivos vimos então solicitar a sua participação neste estudo que será realizado durante o seu internamento no Centro Hospitalar de Leiria, com apoio da Escola Superior de Saúde da Universidade de Aveiro (ESSUA).

Porque é que fui escolhido?

Foi escolhido/a porque é uma pessoa com uma exacerbação aguda da DPOC, que se encontra internado/a no Centro Hospitalar de Leiria. Para o estudo, precisamos de dados de aproximadamente 30 pessoas, com uma condição clínica semelhante à sua, que aceitem participar.

Tenho de participar?

A decisão de participar, ou não, é completamente sua. Se decidir participar vai-lhe ser pedido que assine um formulário de consentimento informado mas, é totalmente livre de desistir a qualquer momento, sem que para tal tenha de dar qualquer justificação. A decisão de desistir ou de não participar, não afetará a qualidade dos serviços de saúde ou qualquer outro, que lhe são prestados agora ou no futuro.

O que me acontecerá caso decida participar?

Se decidir participar, após assinar e entregar aos investigadores o consentimento informado, será feita uma avaliação do seu estado de saúde geral. Primeiro, serão gravados os sons dos seus pulmões durante aproximadamente 20 segundos (2 repetições), com um estetoscópio eletrónico. Seguidamente, ser-lhe-á medido a altura e o peso numa balança. Depois, ser-lhe-á avaliada a força dos seus músculos da respiração e a capacidade respiratória, através de dois testes que consistem em inspirar e soprar para um equipamento, e que demoram breves segundos a realizar a medição. A avaliação da força dos seus músculos da coxa realizar-se-à através de um aparelho que se encosta à perna, é-lhe pedido que realize o máximo de força que conseguir e em aproximadamente 6 segundos, o aparelho indica a força daquele músculo. A força da mão será avaliada com um aparelho de preensão que terá de apertar com o máximo de força que conseguir durante breves segundos. Veremos também a sua tolerância ao exercício através do teste de sentar e levantar de uma cadeira. Mediremos também a quantidade de oxigénio no seu sangue e a sua frequência cardíaca através de um oxímetro (aparelho pequeno que se coloca no seu indicador e nos dá a informação desses valores em segundos). De seguida avaliaremos a sua frequência respiratória observando a sua região abdominal e mediremos a tensão arterial com um medidor de tensão arterial digital. Por último, ser-lhe-á pedido que responda a um questionário para avaliar o seu nível de atividades física e um outro para avaliar o impacto da sua doença no seu dia-a-dia.

Devido à exacerbação, apenas e se o médico que o acompanha achar pertinente, iniciará sessões de reabilitação respiratória durante o seu internamento hospitalar.

Estas avaliações/intervenção serão realizadas no Centro Hospitalar de Leiria, na enfermaria onde se encontra internado, ou caso apresente condições clínicas e seja da sua preferência, poderão ser realizadas no serviço de Medicina Física e de Reabilitação. A duração da avaliação inicial e final será de aproximadamente 45 minutos. No caso de realizar reabilitação respiratória, as sessões terão uma duração aproximada de 20 minutos. Não se antecipa que alguma avaliação ou técnicas de tratamento realizadas provoque qualquer dor

ou desconforto e as mesmas serão sempre realizadas e supervisionadas por profissionais de saúde adequadamente treinados.

Quais são os efeitos secundários, desvantagens e riscos se eu resolver participar?
Não existem efeitos secundários, desvantagens ou riscos de participar no estudo. Os seus sintomas e sinais vitais estarão sempre a ser monitorizados, garantindo a sua segurança e bem-estar. No entanto, na eventualidade de se sentir um pouco cansado(a) durante as avaliações ou tratamentos, intervalos regulares ser-lhe-ão dados de acordo com a sua necessidade.

Quais são os possíveis benefícios se eu resolver participar?
Toda a informação clínica recolhida ser-lhe-á fornecida para que seja do seu conhecimento. Para além disso, a informação obtida neste estudo, através da sua participação, poderá ajudar a melhorar o conhecimento sobre o processo de recupração e os protocolos de reabilitação respiratória em utentes com exacerbação aguda da DPOC hospitalizados.

A minha participação será confidencial?
Toda a informação recolhida no decurso do estudo será mantida estritamente confidencial e mantido o anonimato. Os dados recolhidos serão salvaguardados com um código e palavra-passe, para que ninguém o/a possa identificar. Apenas os investigadores do projeto terão acesso à base de dados e aos seus dados, que estarão fechados num armário à chave, até cinco anos após a realização do estudo. Após esta data, toda a informação será destruída de acordo com as regras da Universidade de Aveiro.

O que acontecerá aos resultados do estudo?
Os resultados do estudo serão analisados e incorporados em Dissertações de Mestrado e Teses de Doutoramento e alguns serão publicados em Jornais Científicos. No entanto, em nenhum momento o Sr./Sra. será identificado/a. Se gostar de obter uma cópia de qualquer relatório ou publicação, por favor diga ao investigador com quem contactar.

Quem é que está a organizar e a financiar o estudo?
Este estudo está a ser realizado no âmbito de uma tese de mestrado em Fisioterapia Respiratória inserida num projeto de investigação financiado pelo Programa Operacional Competitividade e Internacionalização - COMPETE, através do Fundo Europeu de Desenvolvimento Regional - FEDER (POCI-01-0145-FEDER-016701), pela Fundação para a Ciência e Tecnologia (PTDC/DTP-PIC/2284/2014) e parcialmente apoiado pelo COMPETE através do FEDER e da FCT no projeto UID/BIM/04501/2013.

Contactos para mais informações sobre o estudo

Ft. Marta Vieira
Tel.: 912542814
e-mail: *msvieira@ua.pt*

Alda Marques (orientadora)
Tel.: 927992279
e-mail: amarques@ua.pt

Appendix B – Informed Consent

CONSENTIMENTO INFORMADO

LIVRE E ESCLARECIDO PARA PARTICIPAÇÃO EM INVESTIGAÇÃO

Por favor, leia com atenção a seguinte informação. Se achar que algo está incorreto ou que não está claro, não hesite em solicitar mais informações. Se concorda com a proposta que lhe foi feita, queira por favor assinar este documento.

Título do estudo: Efeitos da reabilitação respiratória hospitalar nas exacerbações agudas da doença pulmonar obstrutiva crónica.

O meu nome é Marta Sofia de Almeida Vieira, sou fisioterapeuta e aluna do Mestrado em Fisioterapia – ramo Respiratória na Escola Superior de Saúde da Universidade de Aveiro (ESSUA) e, em conjunto com a minha orientadora, a Prof. Doutora Alda Sofia Pires de Dias Marques, Professora Adjunta e Diretora do Mestrado em Fisioterapia na ESSUA, estamos a desenvolver um estudo que tem como,

principal objetivo: estudar o efeito da reabilitação respiratória em meio hospitalar em utentes com exacerbação aguda da doença pulmonar obstrutiva crónica.

Assim, para que os objetivos do estudo possam ser alcançados com sucesso, vimos por este meio solicitar a sua participação no mesmo. Se aceitar participar, ser-lhe-á pedido que responda a algumas perguntas simples sobre a sua saúde (e.g., quantas vezes recorreu ao hospital no último ano, se tem alguma condição de saúde, se é ou não fumador) e que realize alguns testes para avaliação da sua força muscular e capacidade para realizar esforços. Todos os testes serão supervisionados por profissionais devidamente treinados para o efeito e não se antecipa que os mesmo lhe venham a causar qualquer mal estar. Adicionalmente, se o médico que o acompanha achar necessário, ser-lhe-ão aplicados tratamentos diários de reabilitação respiratória, por fisioterapeutas devidamente treinados, de acordo com os procedimentos já implementados no hospital. Se o médico que o acompanha não achar pertinente realizar reabilitação respiratória, realizará apenas os tratamentos por ele seleccionados. Em qualquer dos casos, à data da sua alta, voltará a ser avaliado, e 3 meses após a sua alta, o seu processo clínico será consultado para verificar entradas no Serviço de Urgência e/ou novos internamentos. Este estudo mereceu parecer favorável da Comissão de Ética e do Conselho de Administração do Centro Hospitalar de Leiria (reunião de 2018.01.09).

A sua participação é voluntária e todas as informações obtidas através destes procedimentos são anónimas e confidenciais e serão apenas utilizadas para fins de investigação, estando em todos os momentos assegurada a sua confidencialidade e anonimato. Neste sentido, em qualquer momento pode interromper a sua participação, sem qualquer tipo de prejuízo.

Caso necessite de algum esclarecimento adicional não hesite em contactar pelo(s):

Tel.: 912542814 E-mail: msvieira@ua.pt - Ft. Marta Vieira

Tel.: 234 372 462 E-mail: amarques@ua.pt - Prof. Doutora Alda Marques

Obrigado pela sua colaboração.

As Investigadoras:

Data:_____/_____/_____

_____ _____

(Prof. Doutora Alda Sofia Pires de Dias Marques) (Marta Sofia de Almeida Vieira)

Declaro ter lido e compreendido este documento, bem como as informações verbais que me foram fornecidas pela pessoa que acima assina. Foi-me garantida a possibilidade de, em qualquer altura, recusar participar neste estudo sem qualquer tipo de consequências. Desta forma, aceito participar neste estudo e permito a utilização de dados, confiando em que apenas serão utilizados para esta investigação e nas garantias de confidencialidade e anonimato que me são dadas pela investigadora.

Nome:_____

Assinatura:_____

Data:_____/_____/_____

Annex I – Ethics Committee and Administrative Broad of *Centro Hospitalar de Leiria* approval

DELIBERAÇÃO DO
Conselho de Administração
Acta nº 01 2018.01.09

18.01.09

CENTRO
HOSPITALAR
LEIRIA

Exmo. Senhor
Presidente do Conselho de Administração
Centro Hospitalar de Leiria, E.P.E.

Para CA.

Alexandra Borges
Vogal Executiva
2017/12/22

CI - Centro de Investigação
Ref.ª 61/2017

Leiria, 20 de dezembro de 2017

Assunto: Estudo "Efeitos da reabilitação respiratória hospitalar nas exacerbações agudas da doença pulmonar obstrutiva crónica (DPOC) - Projectos GENIAL: Marcadores Genéticos e Clínicos na Trajetória da DPOC", submetido por Marta Vieira, a desenvolver nos Serviço de MFR, Pneumologia, Medicina 1 e 2

De acordo com o Procedimento Interno "Aprovação de estudos e projetos de Investigação", em vigor desde 2016.03.07, informa-se que o estudo mencionado em epígrafe está devidamente instruído de acordo com os elementos assinalados na Listagem de Documentos e Validação, em anexo.

Mais se informa que o presente estudo obteve parecer favorável pela Comissão de Ética, de acordo com a Ata n.º 08 de 2017.12.12. Neste sentido, submete-se o pedido anexo para decisão final do Conselho de Administração.

Os meus cumprimentos.

O COORDENADOR DO CENTRO DE INVESTIGAÇÃO,

(JOÃO MORAIS)

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Enviado. Email de notificação ao CI 18.01.10 AG

11-01-2018 SC.